Co-current Filtrate Flow in TFF and reverse TFF (rTFF)

Levitronix Seminar

Speakers/Inventors: Patrick Romann and Antony Sibilia

6-March-2024

Glossary

Better Pumps for Better Yield!

TFF	Tangential Flow Filtration
rTFF	Reverse Tangential Flow Filtration
ATF	Alternating Tangential Flow Filtration
TMP	Transmembrane Pressure
HPTFF	High-Performance Tangential Flow Filtration
PTR	Pressure Transmitter Retentate Loop
PTF	Pressure Transmitter Filtrate Loop
PTA	Pressure Transmitter Additional (directly connected to filtrate of Hollow fiber module)
DeltaP	Delta Pressure
HF	Hollow Fiber Module
FM	Flow Meter
CDR	Centrifugal Discharge Pump in Retentate Loop
CDF	Centrifugal Discharge Pump in Filtrate Loop
PD	Pressure Drop
scTFF	Stepping Co-Current Filtrate Flow Tangential Flow Filtration
rscTFF	Reverse Stepping Co-Current Filtrate Flow Tangential Flow Filtration

Content

Better Pumps for Better Yield!

- Motivation
- Background and Theory
  - Comparison of TFF and ATF
  - Comparison of TFF and rTFF
  - Starling Recirculation in hollow fiber filters
- Co-current Filtrate Flow in TFF
  - High-Performance TFF (HPTFF) Principle
  - System Setup and Control Strategy (DeltaP Control vs. Slope Control)
  - Stepping co-current TFF (scTFF)
- rTFF Strategies
  - Setup, Bubble removal considerations, Cycle time

Motivation

Better Pumps for Better Yield!

- **Goal is Process Performance Improvement of TFF applications in upstream (incl. Perfusion) and downstream applications with use of TFF filter modules/membranes.**
- **Focus on so-called co-flow setups with recirculation flow via permeate (filtrate connections of TFF module).**

Background and Theory

TFF, ATF and rTFF

Possible Explanation for Bad TFF Performance

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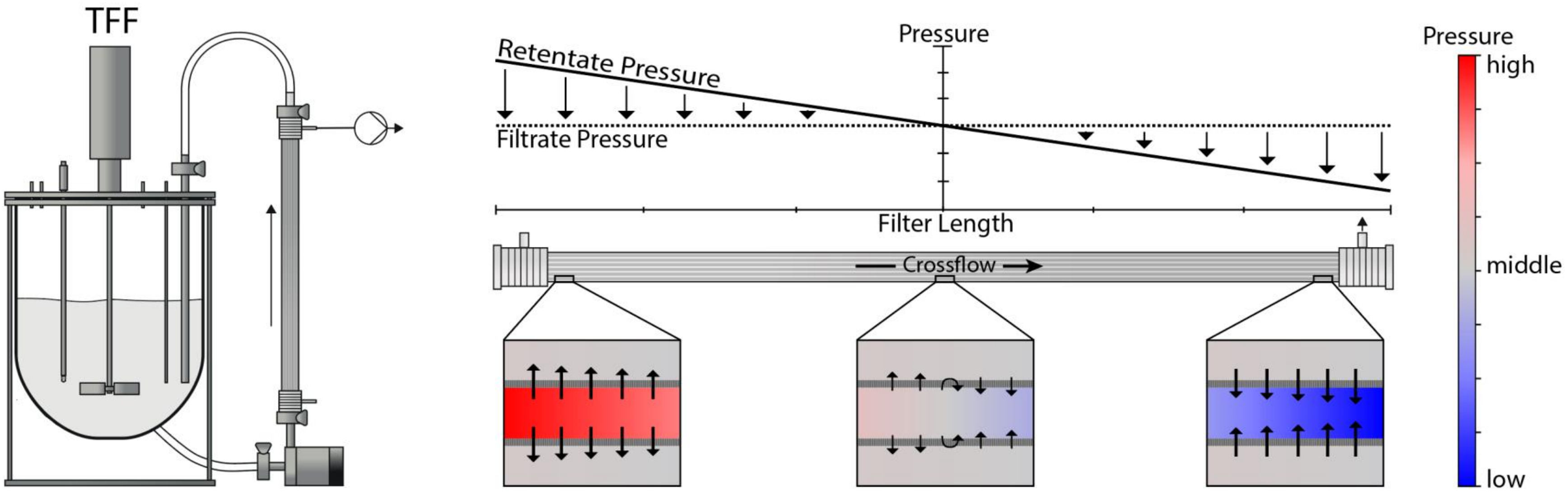
- Pressure drop along filter module → TMP changes



Ref[1]

Possible Explanation for Bad TFF Performance

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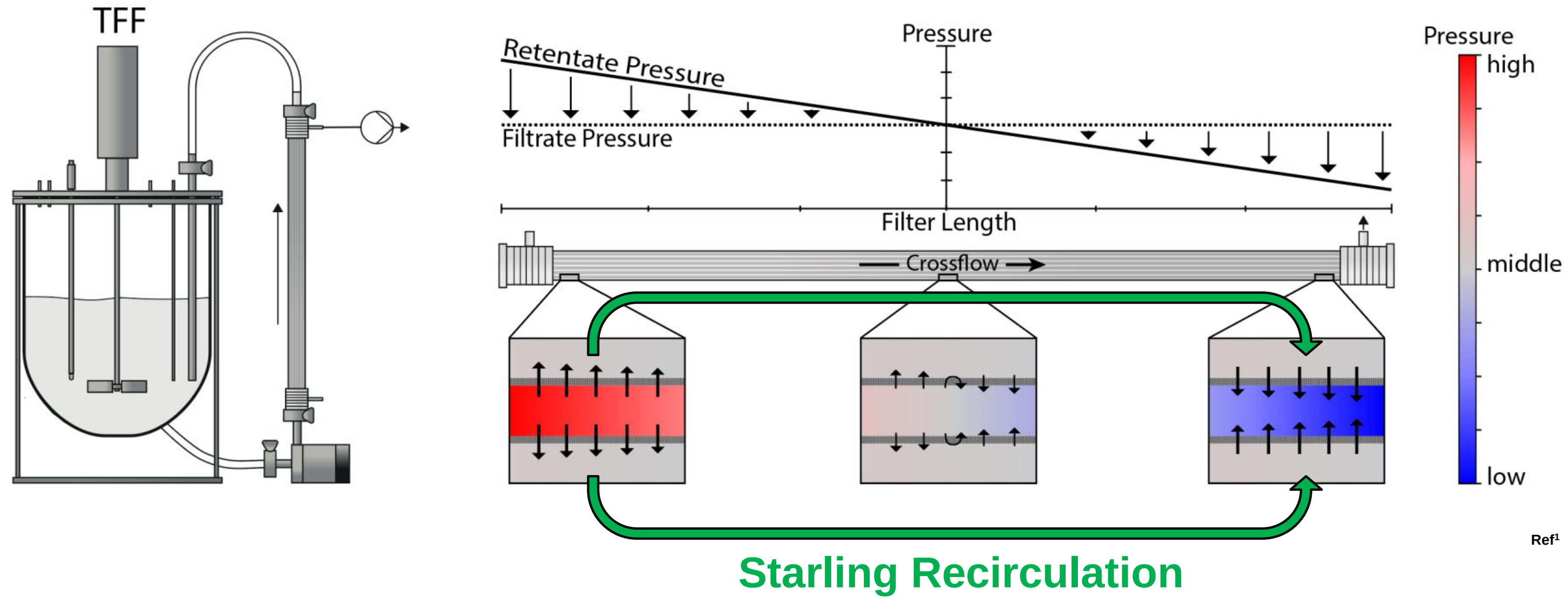
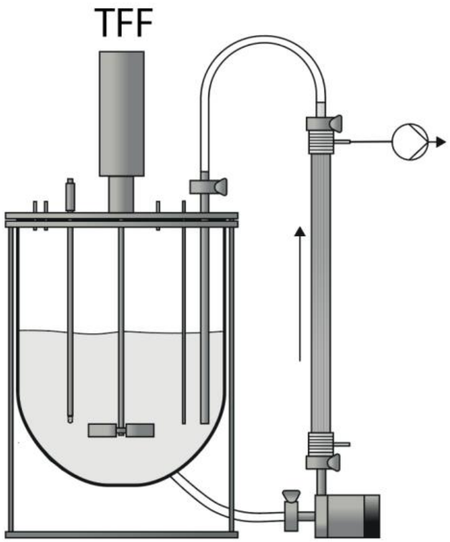
- Pressure drop along filter module → TMP changes
- Starling Recirculation

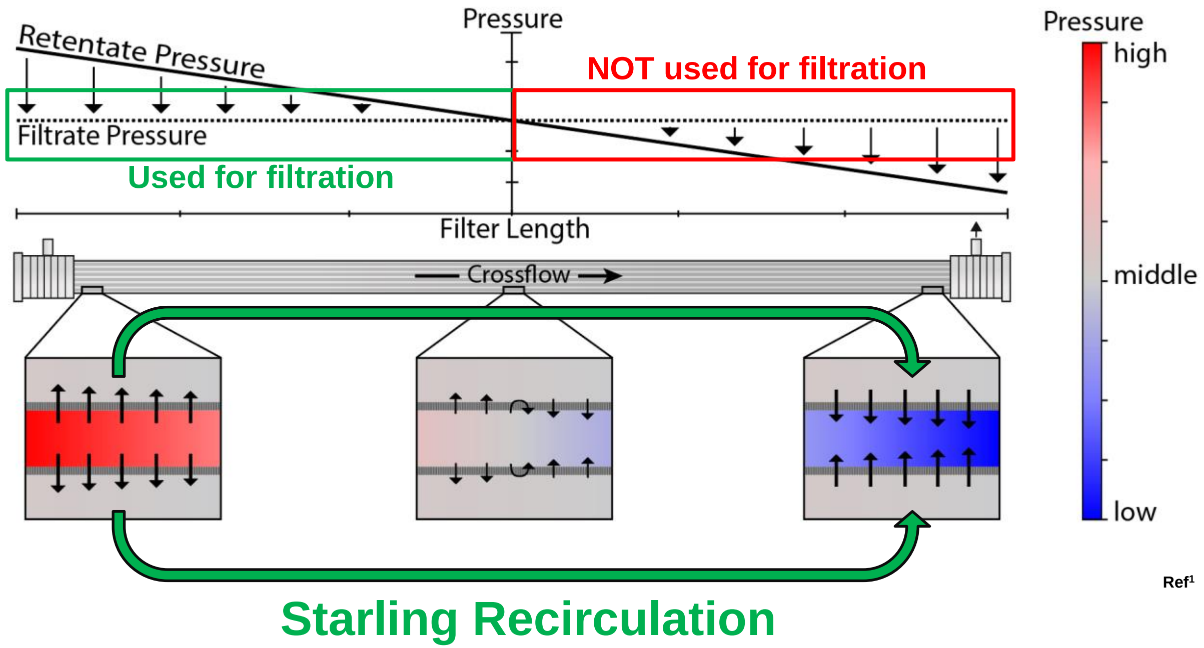


Ref[1]

Possible Explanation for Bad TFF Performance

- Pressure drop along filter module → TMP changes
- Starling Recirculation
- Unidirectional crossflow: only first half of filter used





Ref[1]

Explanation for Better rTFF Performance

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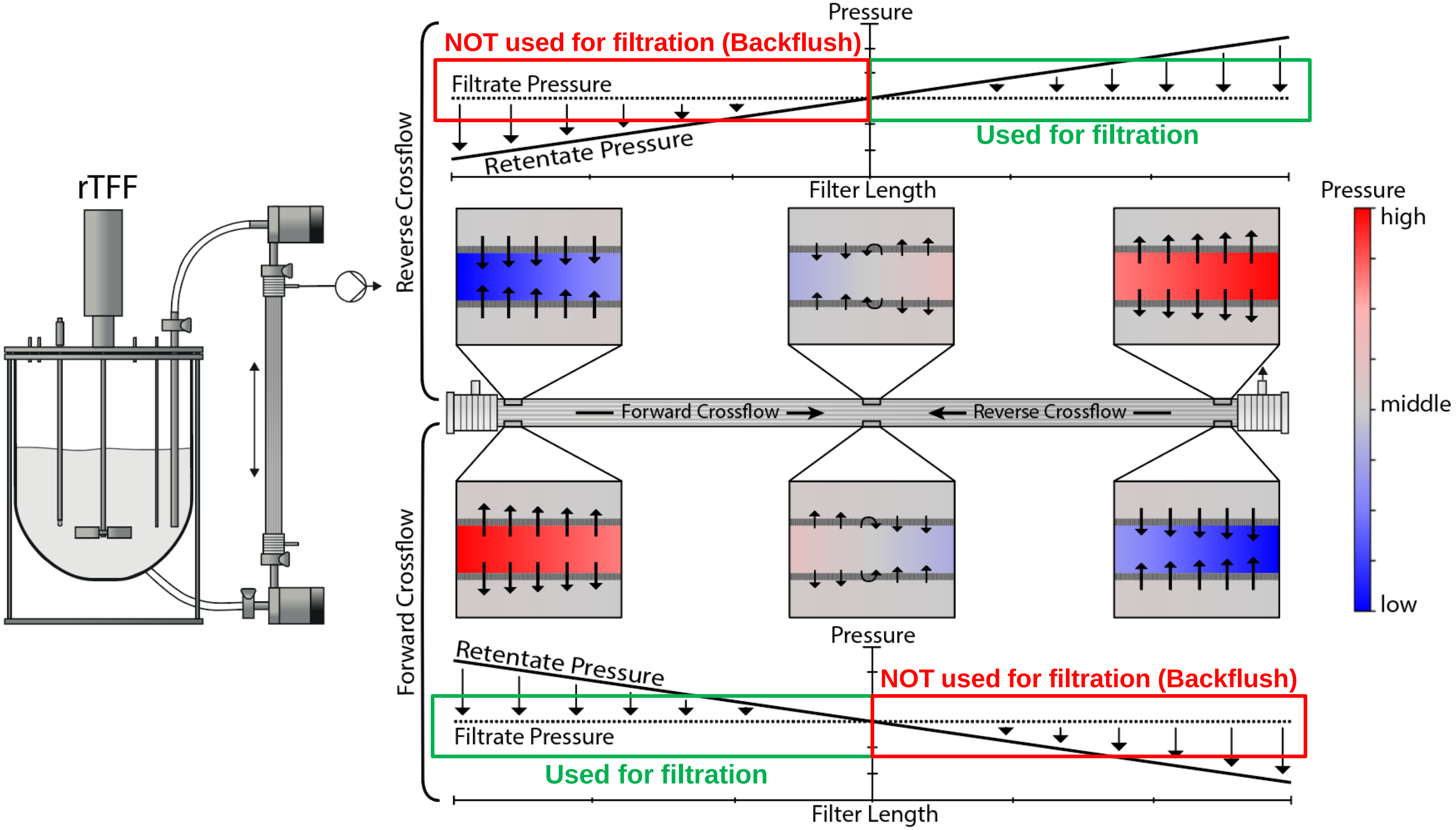

Ref[1]

Similar to TFF:

- Pressure drop along filter
- Starling Recirculation

Difference to TFF:

- Alternating crossflow
- Alternating Starling Recirculation (Backflush)

Is the Backflush only for the Good?

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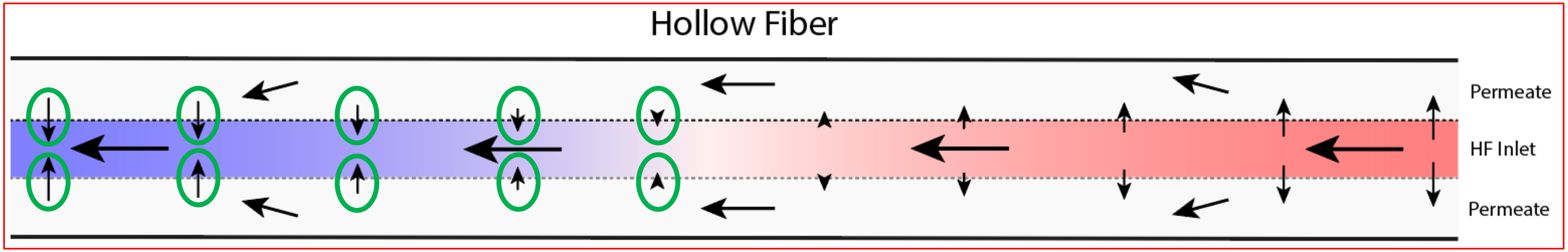
Backflush:

- Backflush: permeate back into filter (filter outlet side)



Is the Backflush only for the Good?

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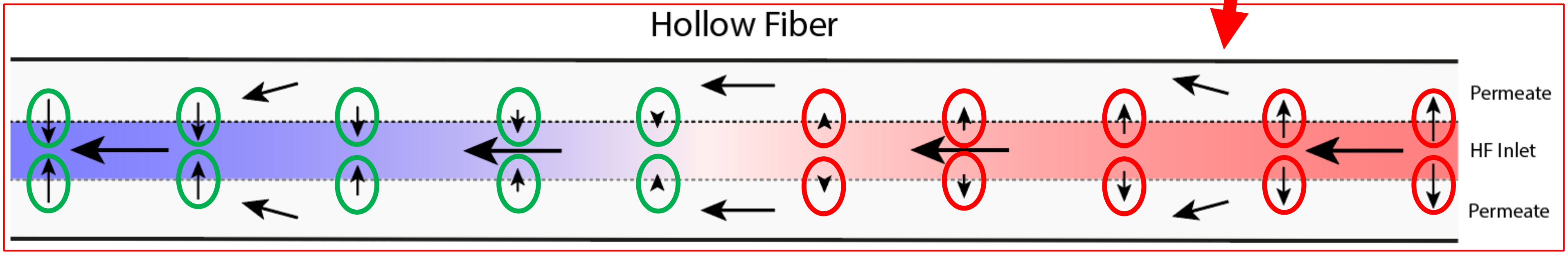
Backflush:

- Backflush: permeate back into filter (filter outlet side)
- Requires also filtrate generation (filter inlet side)

Enormous «unnecessary» flux across membrane and back (filter used much more as actually required for harvesting



Is the Backflush only for the Good?

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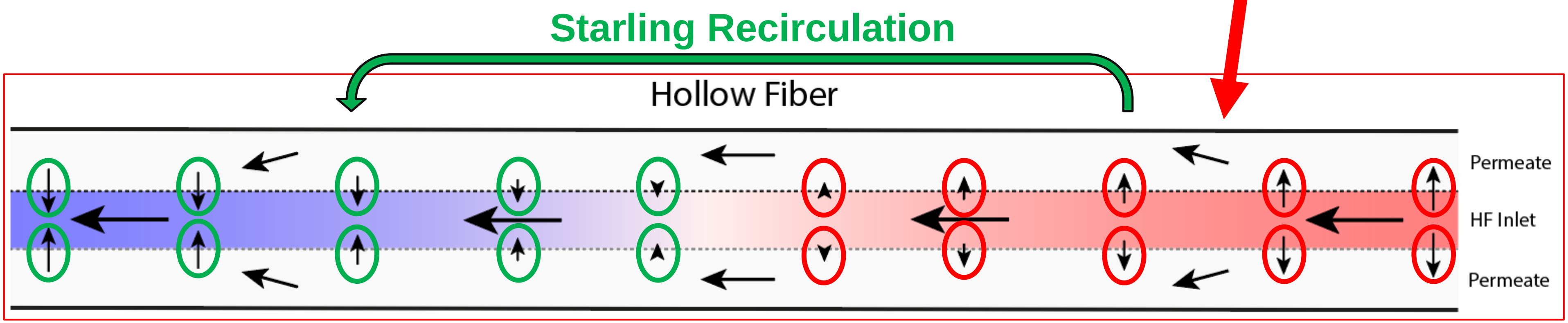
Backflush:

- Backflush: permeate back into filter (filter outlet side)
- Requires also filtrate generation (filter inlet side)
- Backflush **10-100x** larger than permeate flow (actually harvested)

Enormous «unnecessary» flux across membrane and back (filter used much more as actually required for harvesting)



→ How can we reduce Starling Recirculation to improve TFF and rTFF (ATF)?

Co-current Filtrate Flow

Theory

Reducing Starling Recirculation

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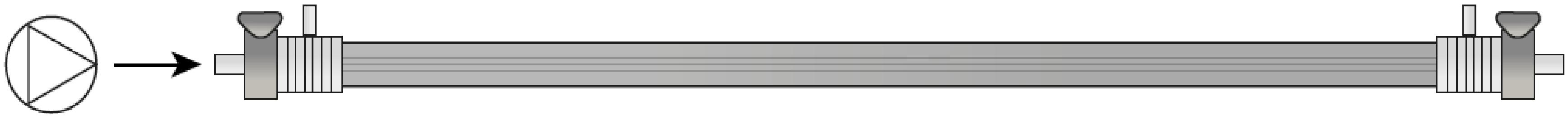
→ How can we reduce Starling Recirculation to improve TFF and rTFF (ATF)?



Culture viscosity (reduce):

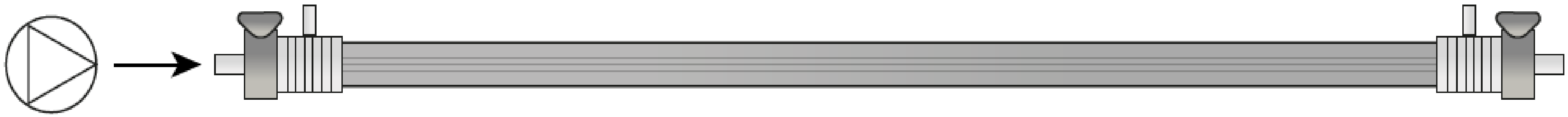
- Increases pressure drop

Reducing Starling Recirculation

→ How can we reduce Starling Recirculation to improve TFF and rTFF (ATF)?

Crossflow velocity (reduce):

- Increases pressure drop
- Limitation: restriction to low crossflows



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Reducing Starling Recirculation

Better Pumps for Better Yield!

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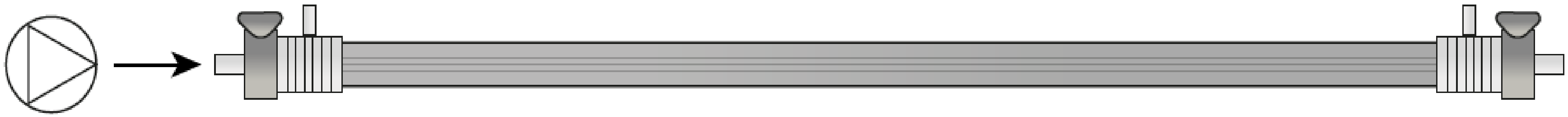


Culture viscosity (reduce):

- Increases pressure drop

Filter length (reduce):

- Increases pressure drop
- Limitation: restriction to shorther filters / parallel setups

Reducing Starling Recirculation

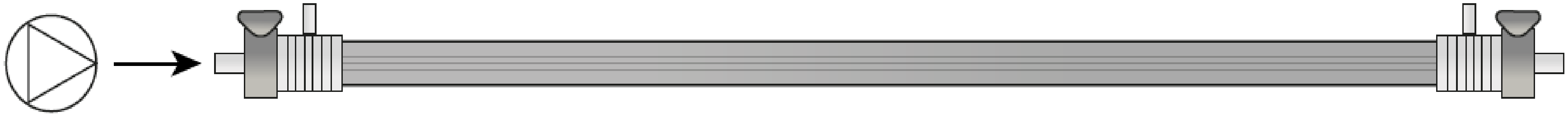
→ How can we reduce Starling Recirculation to improve TFF and rTFF (ATF)?

Crossflow velocity (reduce):

- Increases pressure drop
- Limitation: restriction to low crossflows

Fiber diameter (increase):

- Small diameters increase pressure drop
- Large diameters reduce membrane surface



Culture viscosity (reduce):

- Increases pressure drop

Filter length (reduce):

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- Limitation: restriction to shorther filters / parallel setups

Reducing Starling Recirculation

Better Pumps for Better Yield!

→ How can we reduce Starling Recirculation to improve TFF and rTFF (ATF)?

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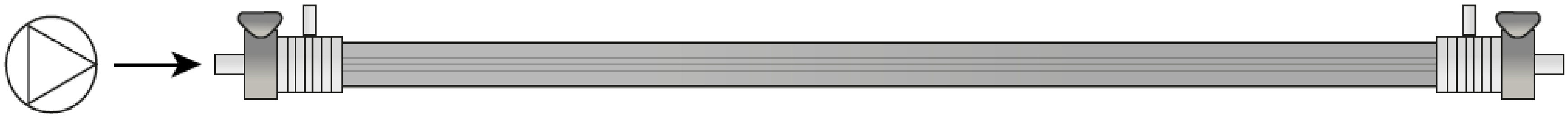


Culture viscosity (reduce):
- Increases pressure drop

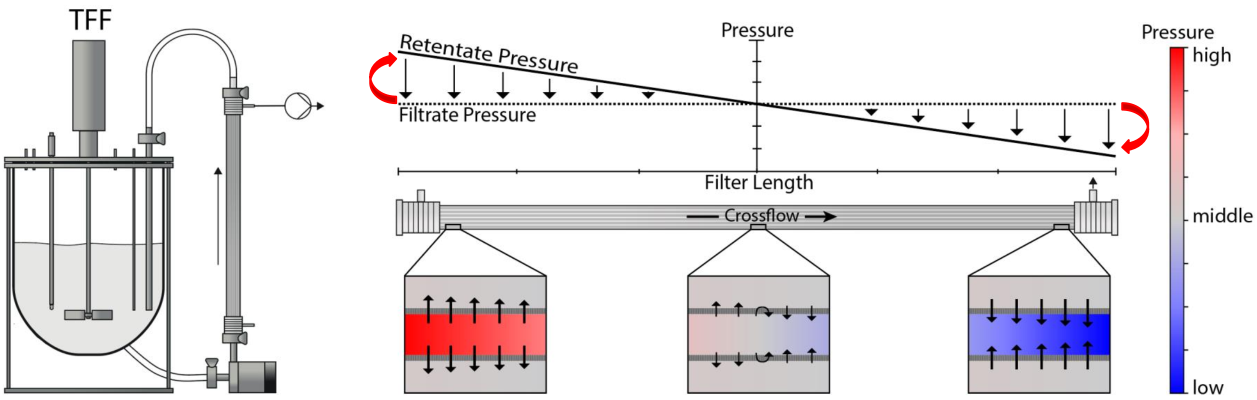
Filter length (reduce):
- Increases pressure drop
- Limitation: restriction to shorther filters / parallel setups

Membrane pore size (reduce):
- Larger pores reduce membrane resistance
- Increase in Starling flow

→ We are very restricted with changing the above factors

Another Way to Reduce Starling Recirculation

Better Pumps for Better Yield!



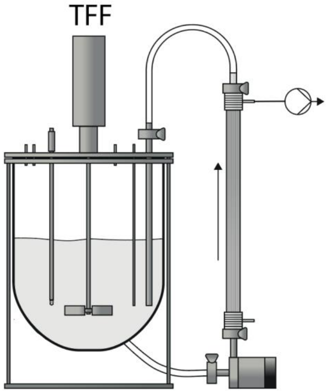
Ref[1]

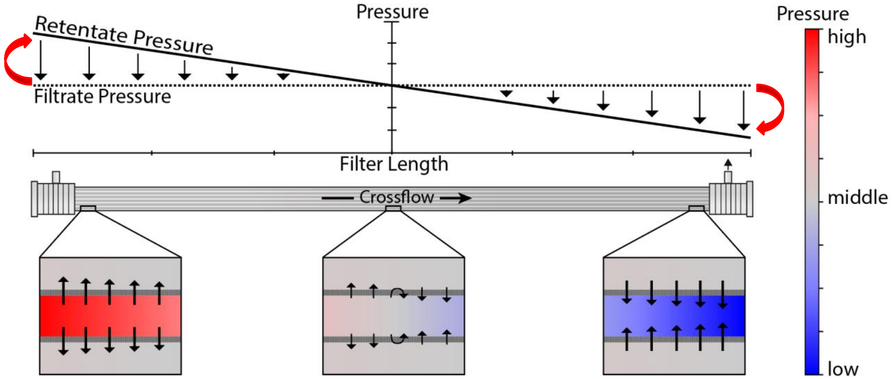
Idea:

- Establish filtrate pressure gradient
- Match filtrate and retentate pressure
- Eliminate Starling Recirculation

Another Way to Reduce Starling Recirculation

Better Pumps for Better Yield!

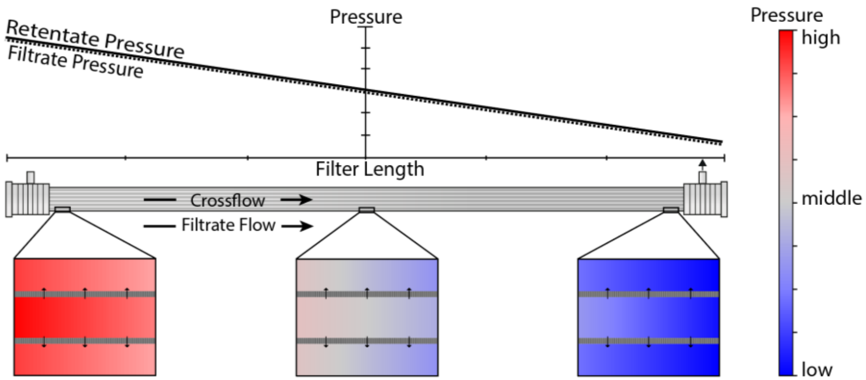




Idea:

- Establish filtrate pressure gradient
- Match filtrate and retentate pressure
- Eliminate Starling Recirculation

?



Ref[1]

Co-current Filtrate Flow: HPTFF

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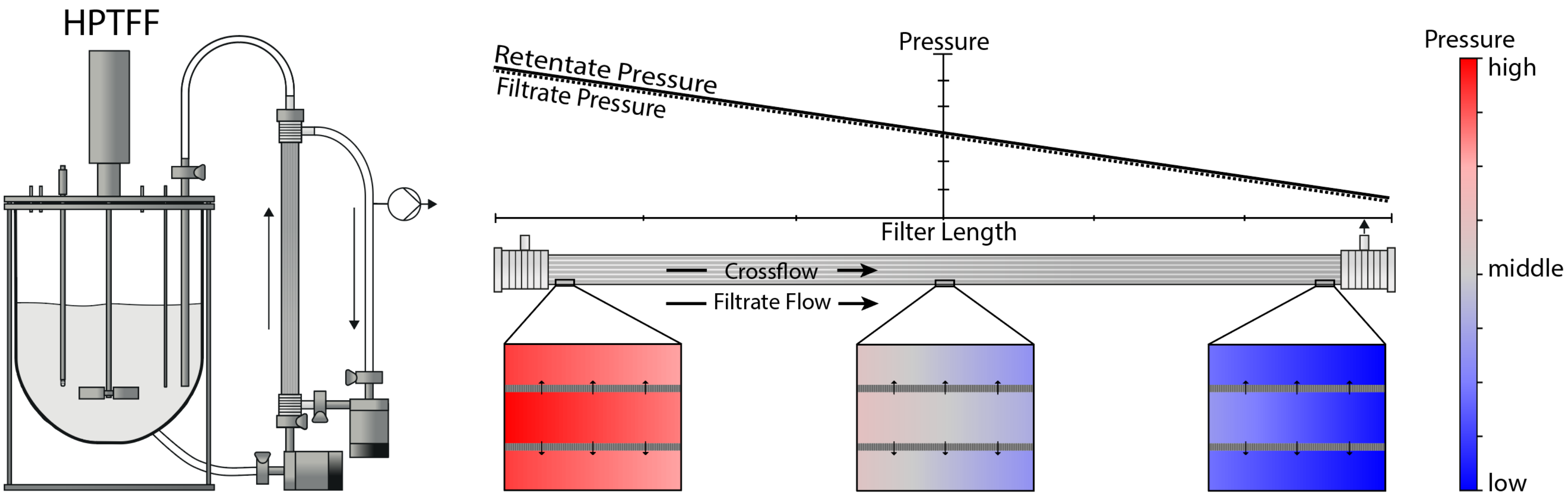
High-performance TFF (HPTFF)



Ref[1]

- Co-current filtrate flow (Levitronix pump)
- Pressure drop on filtrate side
- No TMP across entire membrane (almost)

→ No Starling Recirculation

The Power of Co-current Filtrate Flow

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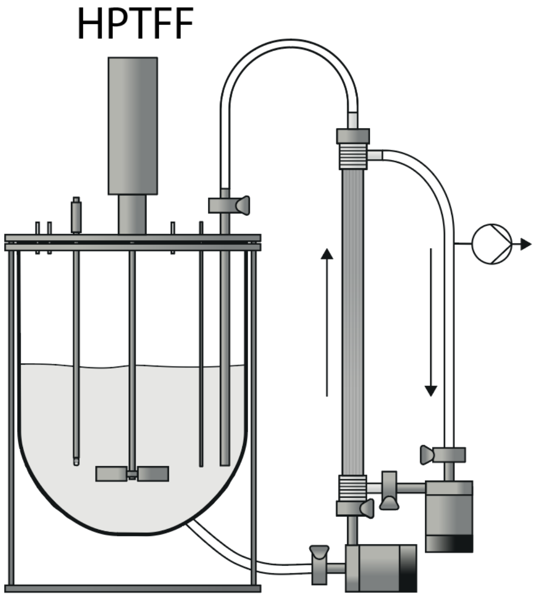
→ We don't decrease pressure drop, but we match filtrate pressure drop



More flexibility for filtration:

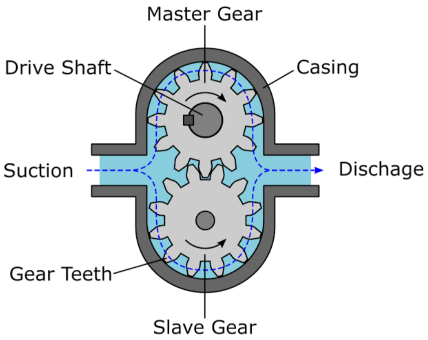
▪ Crossflow velocity	(all ranges possible)
▪ Fiber Diameter	(also small possible)
▪ Higher Culture Viscosity	(increases co-current flow)
▪ Filter Length	(long filters feasible)
▪ Membrane Pore Size	(larger pores possible)

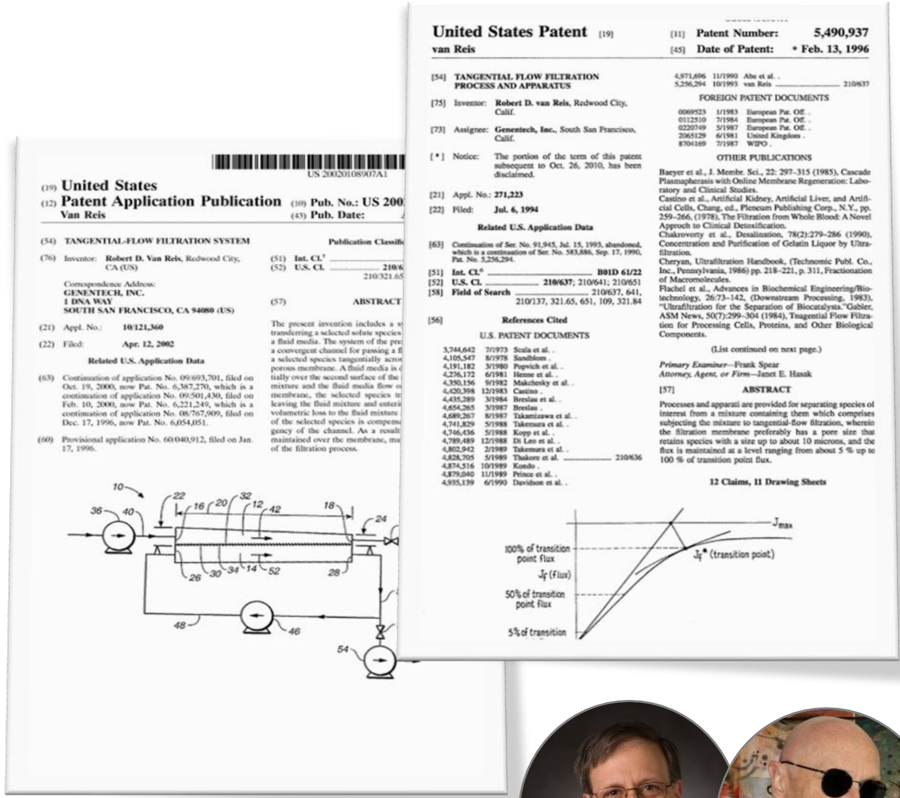
→ simply co-current filtrate flow must be adjusted

HPTFF, a Sleeping Beauty

Patents 5,490,937 & US 2002/0108907

- 1996 patented for DSP
- Idea to create uniform TMP distribution
- Goal to separate proteins by size
- Realized with gear pumps




United States Patent [19] van Reis
[11] Patent Number: 5,490,937
[45] Date of Patent: * Feb. 13, 1996
[54] TANGENTIAL FLOW FILTRATION PROCESS AND APPARATUS
[75] Inventor: Robert D. van Reis, Redwood City, Calif.
[73] Assignee: Genentech, Inc., South San Francisco, Calif.
[21] Appl. No.: 271,223
[22] Filed: Jul. 6, 1994
[57] ABSTRACT
Processes and apparati are provided for separating species of interest from a mixture containing them which comprises subjecting the mixture to tangential-flow filtration, wherein the filtration membrane preferably has a pore size that retains species with a size up to about 10 microns, and the flux is maintained at a level ranging from about 5 % up to 100 % of transition point flux.
12 Claims, 11 Drawing Sheets

(19) United States
(12) Patent Application Publication
Van Reis
(54) TANGENTIAL-FLOW FILTRATION SYSTEM
(76) Inventor: Robert D. Van Reis, Redwood City, CA (US)
(22) Filed: Apr. 12, 2002

Co-current Filtrate Flow

System Setup and Control Strategy

HPTFF: System Setup

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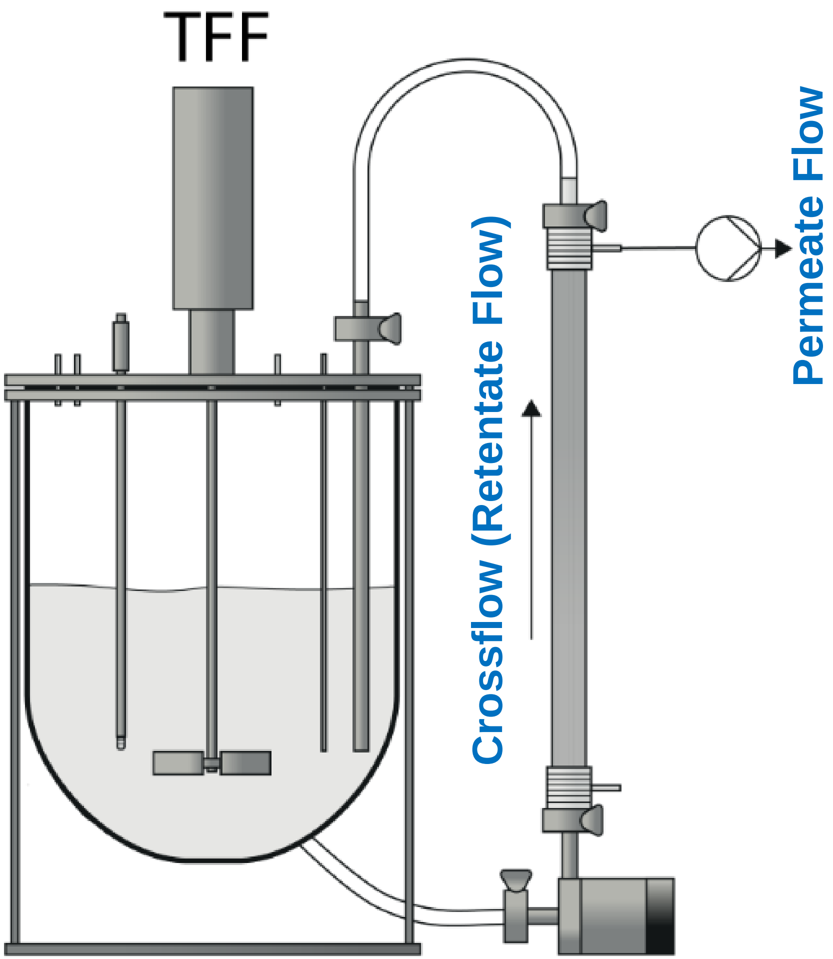

System Setup:

- Retentate pump (Levitronix)

HPTFF: System Setup

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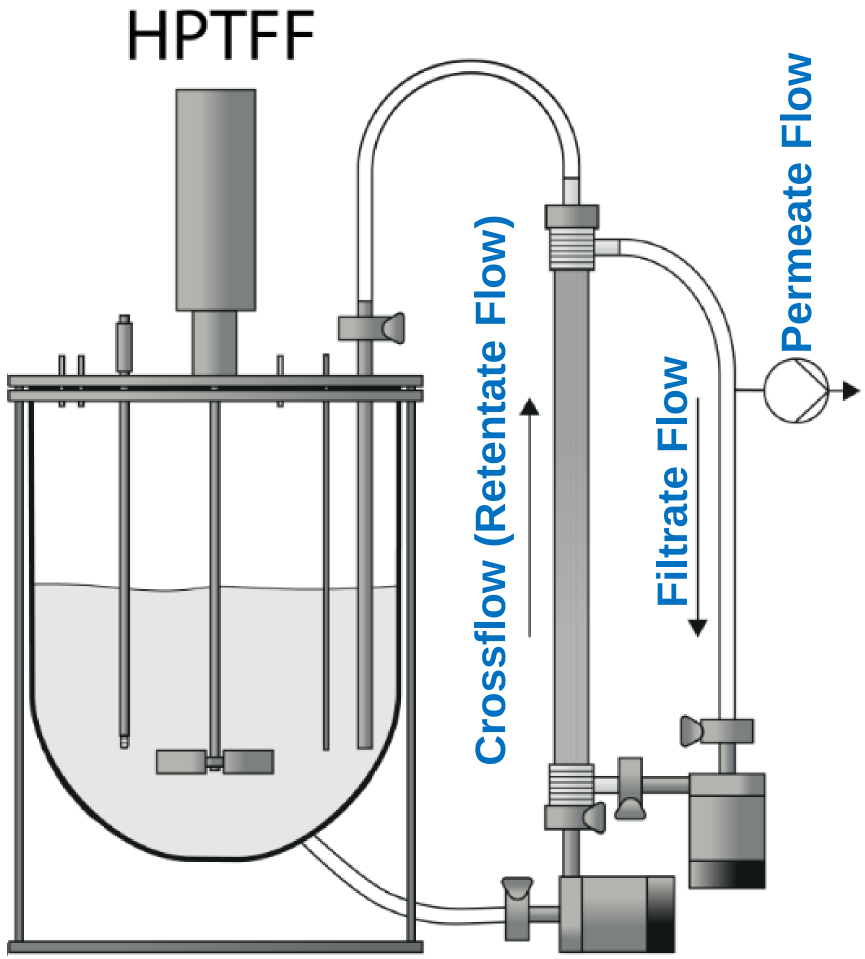
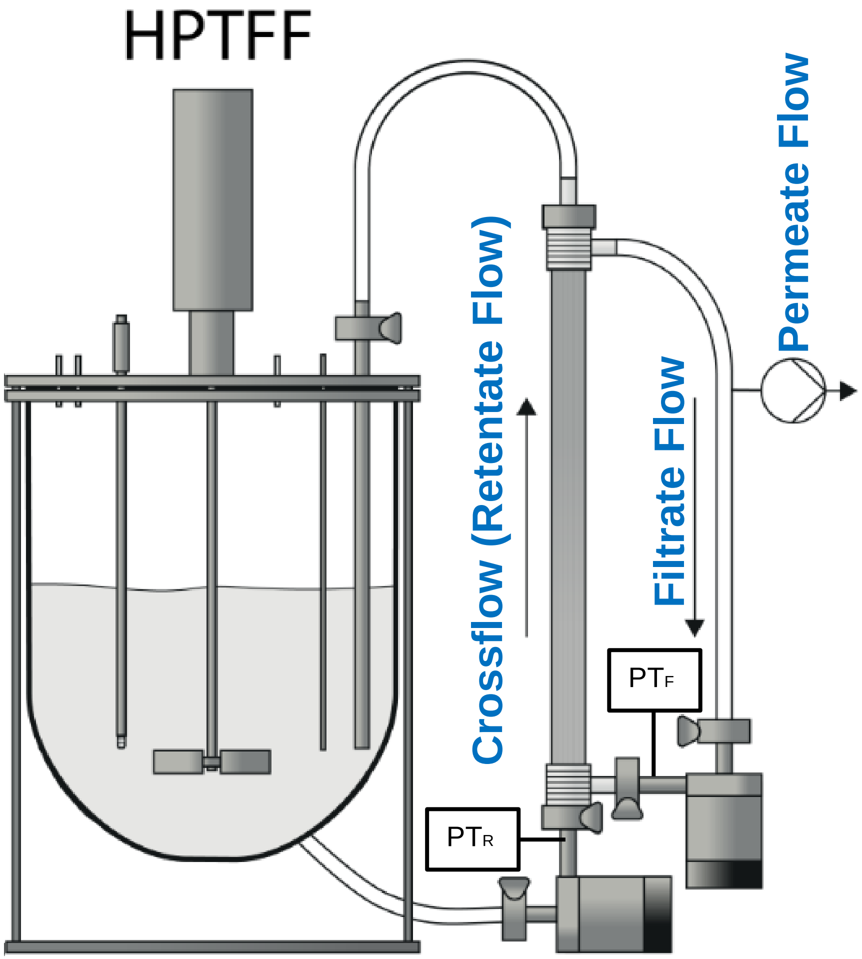


System Setup:

- Retentate pump (Levitronix)
- Filtrate Loop Pump (Levitronix)

HPTFF: System Setup

Better Pumps for Better Yield!



System Setup:

- Retentate pump (Levitronix)
- Filtrate Loop Pump (Levitronix)
- Pressure Sensors (PendoTech)
  - PT_{Rin}: Retentate Inlet
  - PT_{Fin}: Filtrate Inlet

HPTFF: System Setup

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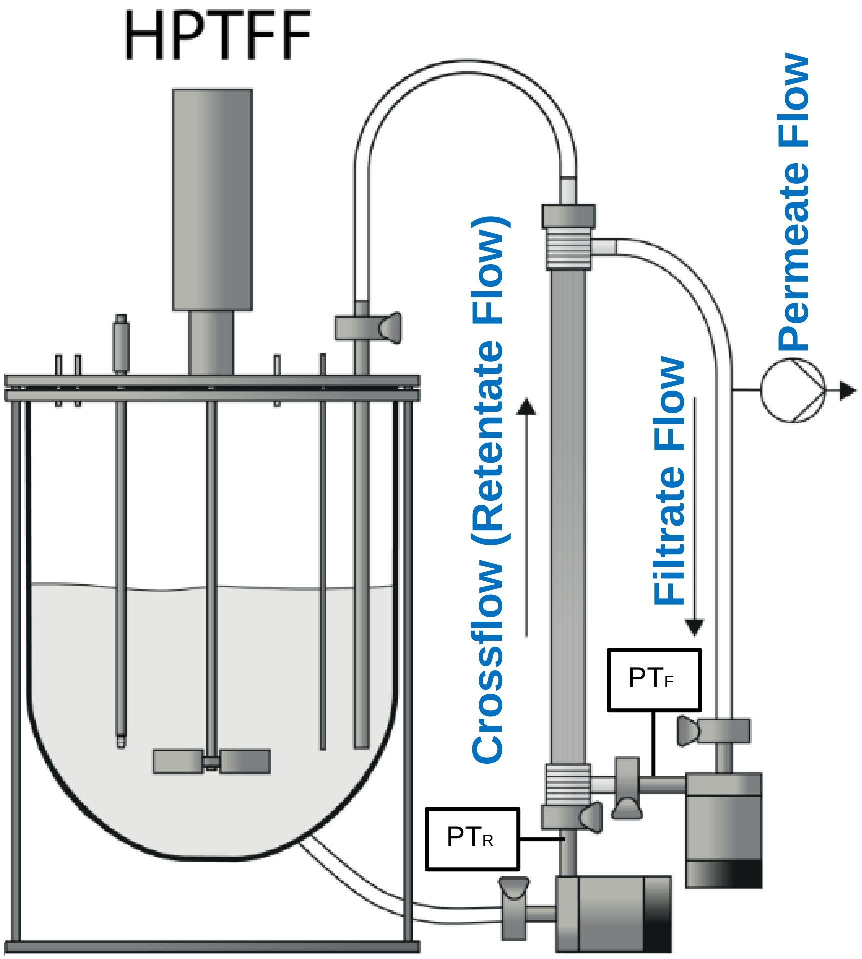

System Setup:

- Retentate pump (Levitronix)
- Filtrate Loop Pump (Levitronix)
- Pressure Sensors (PendoTech)
  - PT_{Rin}: Retentate Inlet
  - PT_{Fin}: Filtrate Inlet
- Optional:
  - Flow Sensors
  - Further Pressure Sensors

HPTFF: System Setup

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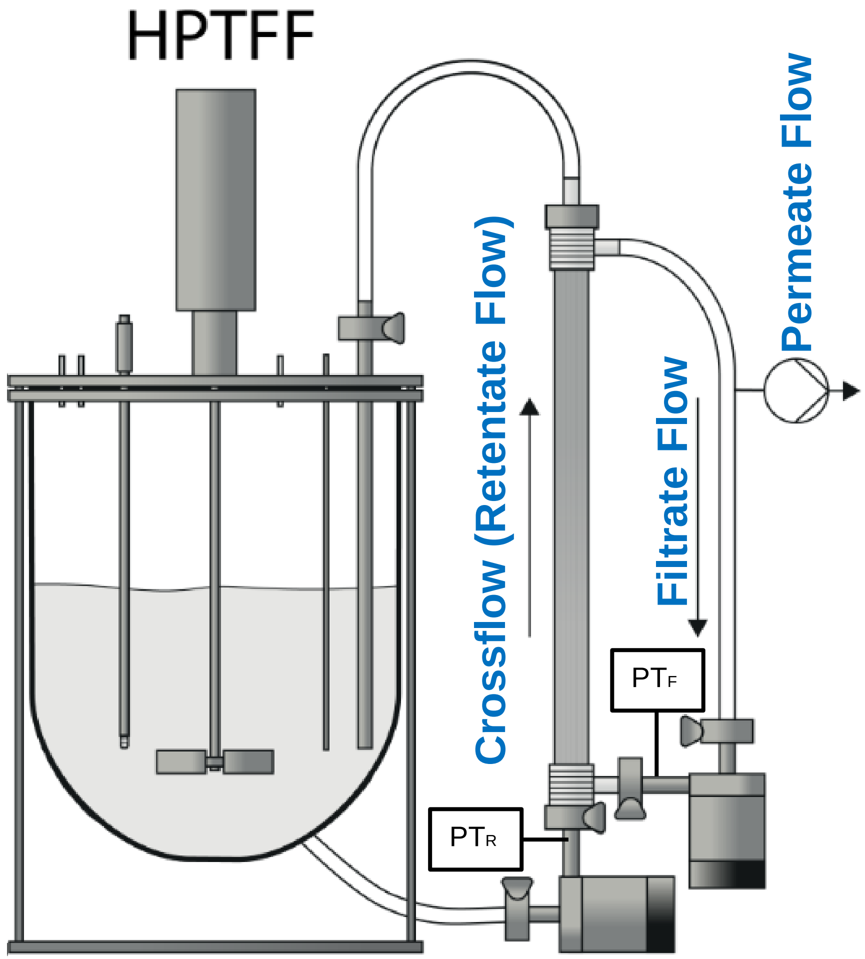
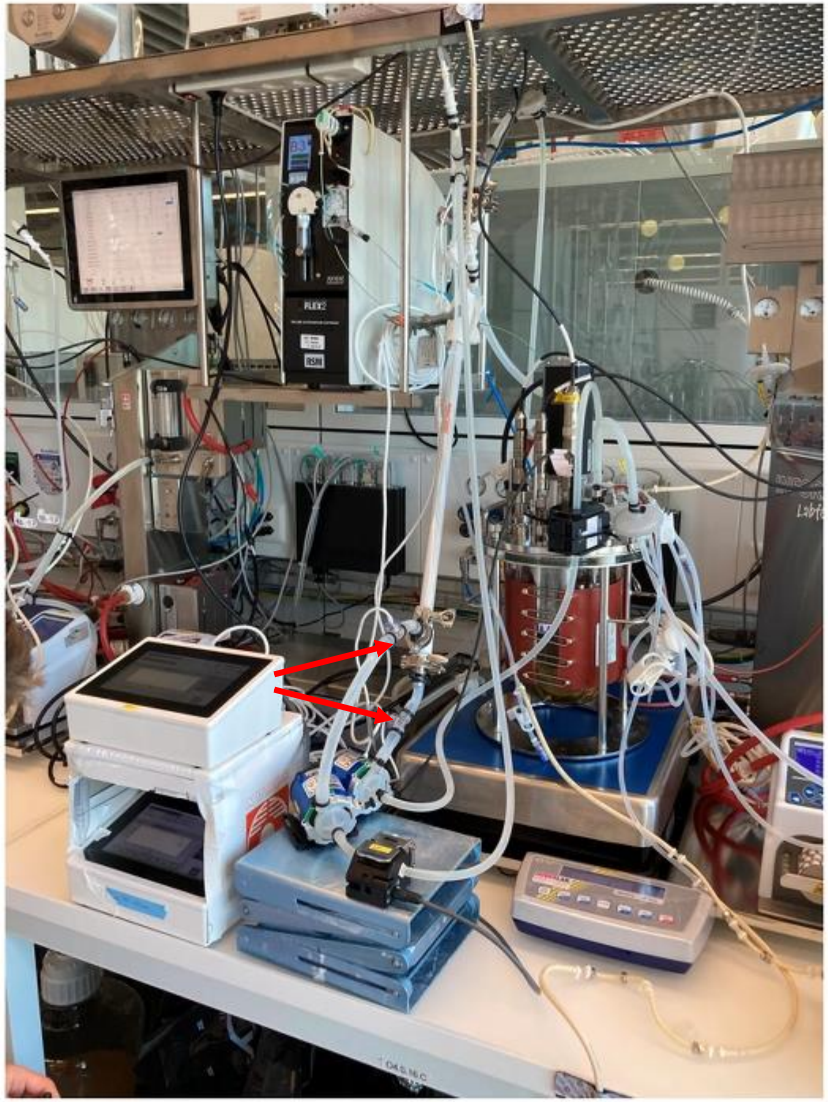
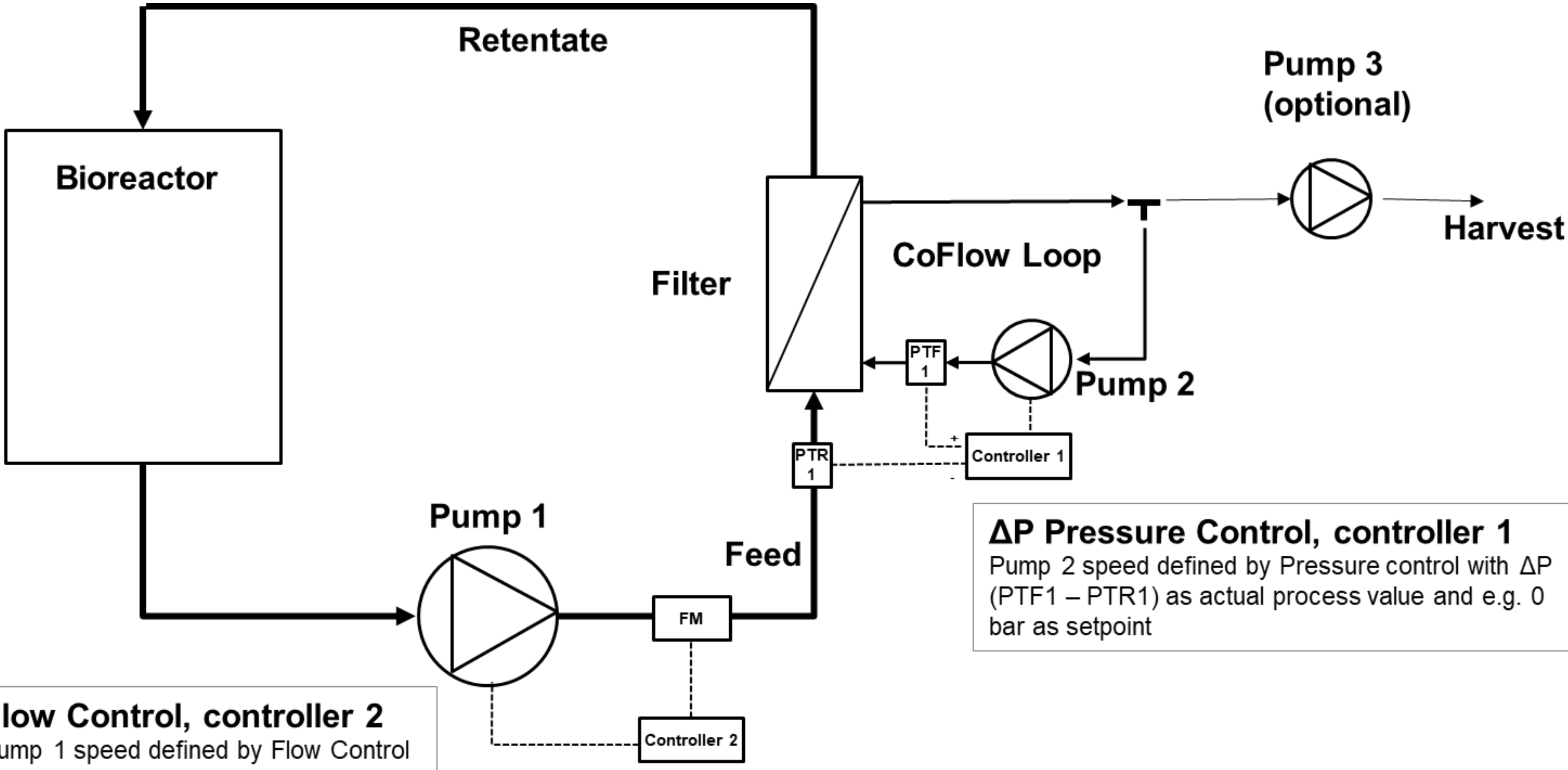




Source: FHNW

HPTFF Control Strategy

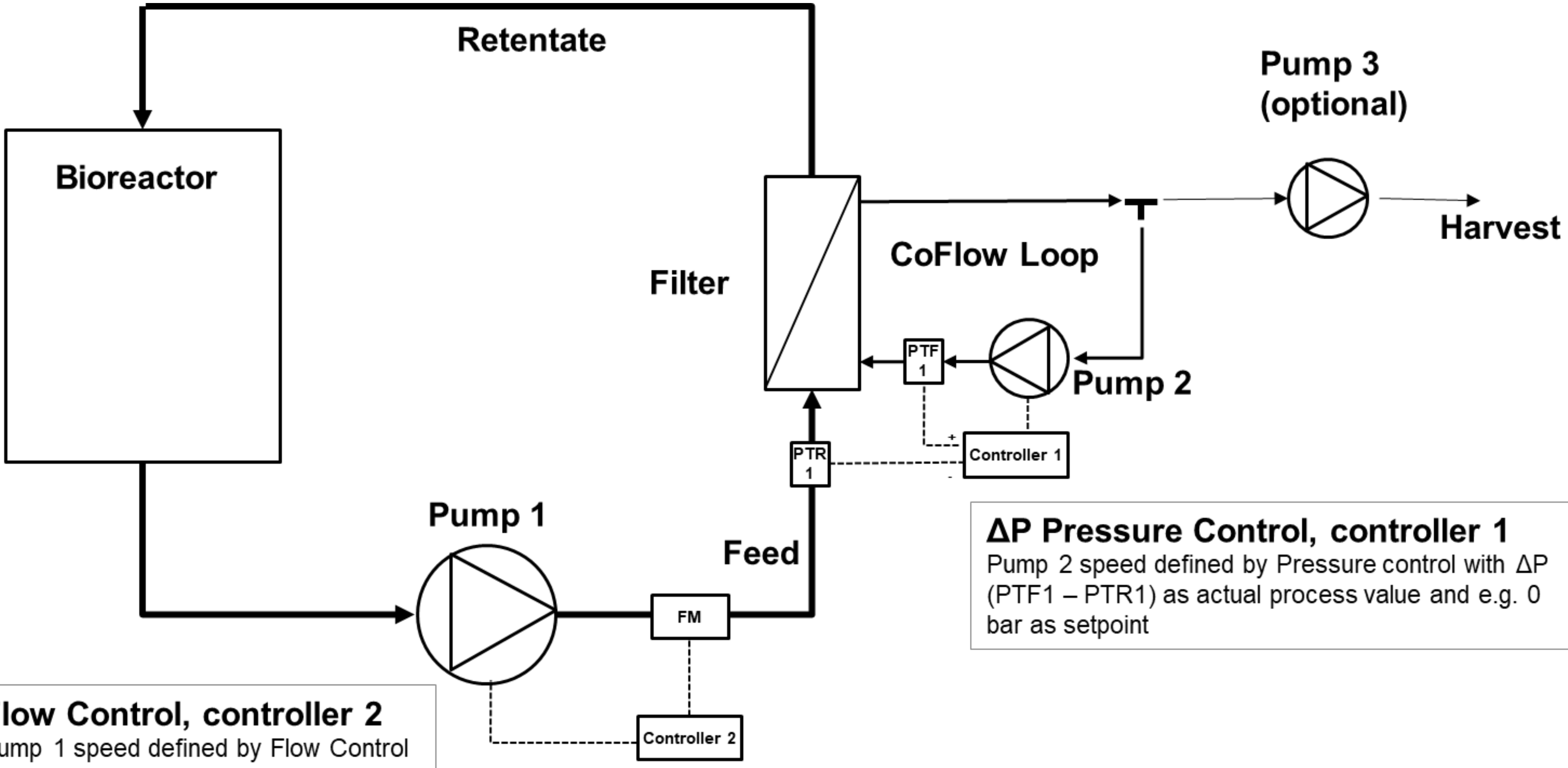


ΔP Pressure Control, controller 1
Pump 2 speed defined by Pressure control with ΔP (PTF1 – PTR1) as actual process value and e.g. 0 bar as setpoint

Flow Control, controller 2
Pump 1 speed defined by Flow Control with FM as actual process value and required crossflow as setpoint

HPTFF Control Strategy

Better Pumps for Better Yield!



ΔP Pressure Control, controller 1
Pump 2 speed defined by Pressure control with ΔP (PTF1 – PTR1) as actual process value and e.g. 0 bar as setpoint

Flow Control, controller 2
Pump 1 speed defined by Flow Control with FM as actual process value and required crossflow as setpoint

→ But how to define the delta?

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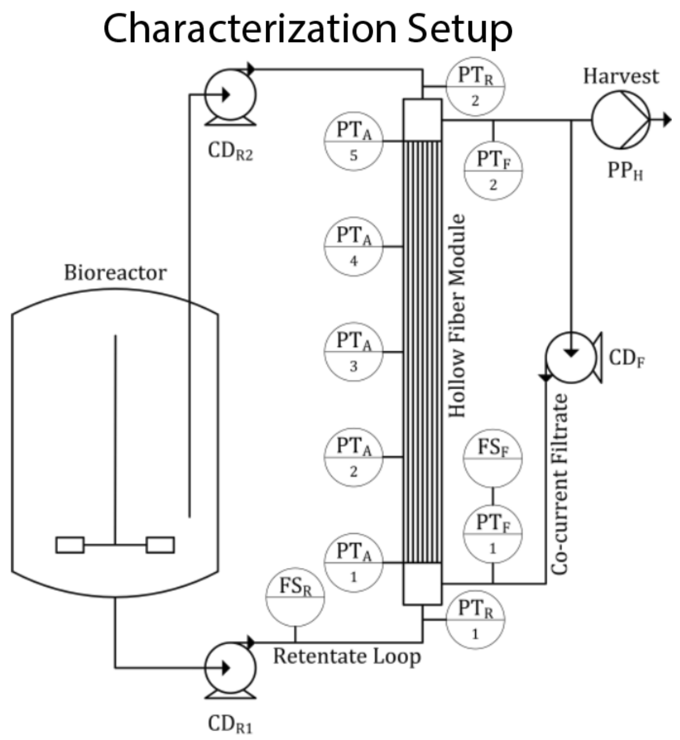
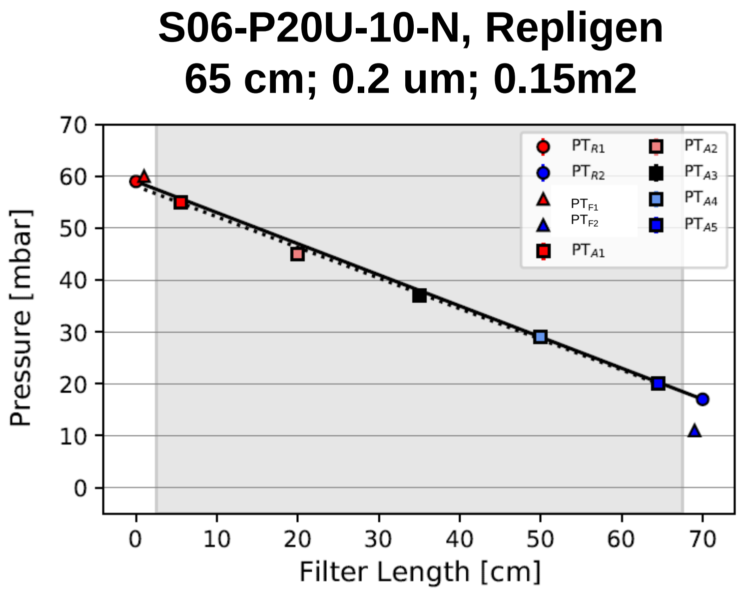
HPTFF Control Strategy: Delta Pressure

→ Delta Pressure Setpoint must be determined! (water characterization)





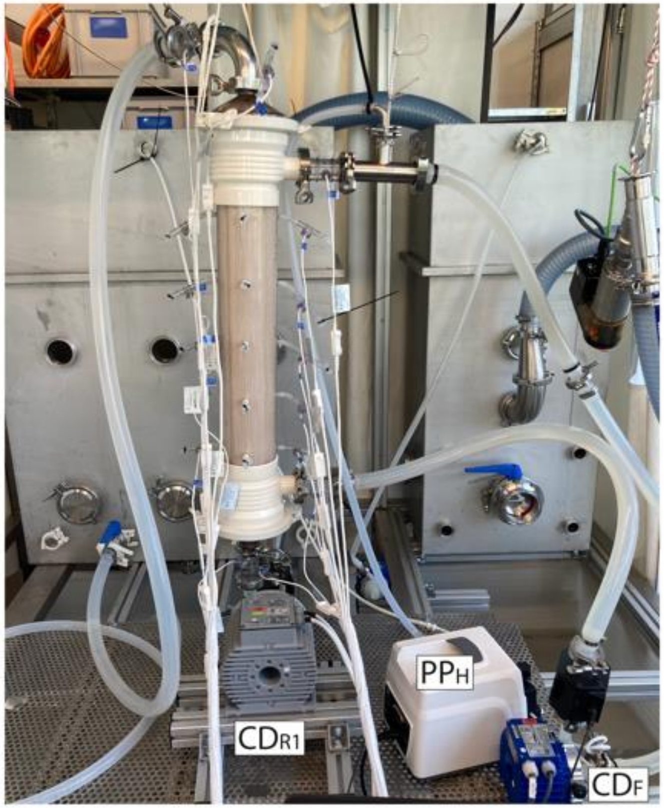
Ref[1]

→ Delta Pressure Setpoint = 0 mbar

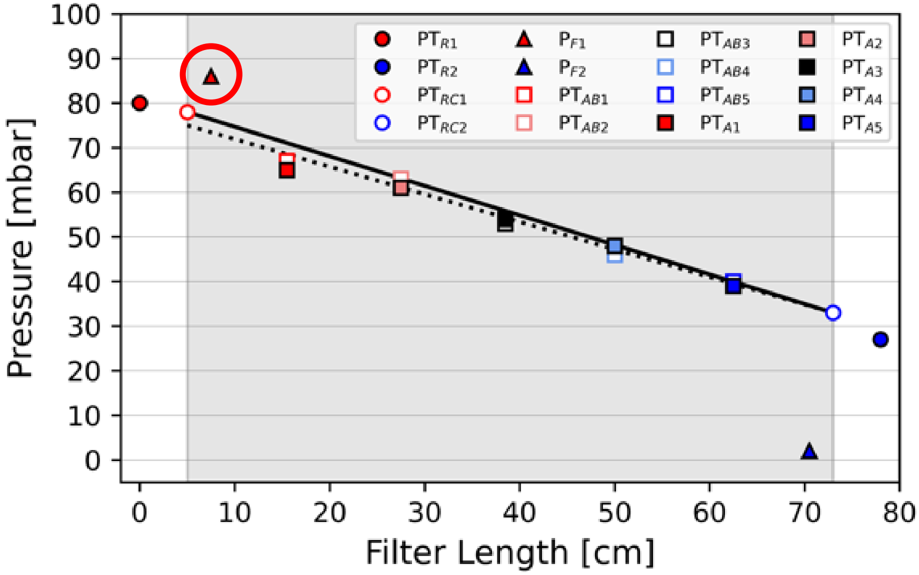
HPTFF Control Strategy: Delta Pressure

Better Pumps for Better Yield!

→ Delta Pressure Setpoint must be determined! (water characterization)



X06-P20U-10, Repligen
70 cm: 0.2 um: 7.15m2



Ref[1]

→ Delta Pressure Setpoint = +5 mbar

→ turbulences might be responsible for pressure drifts (not fully understood)

What happens if we would control to zero diff pressure in this specific case?

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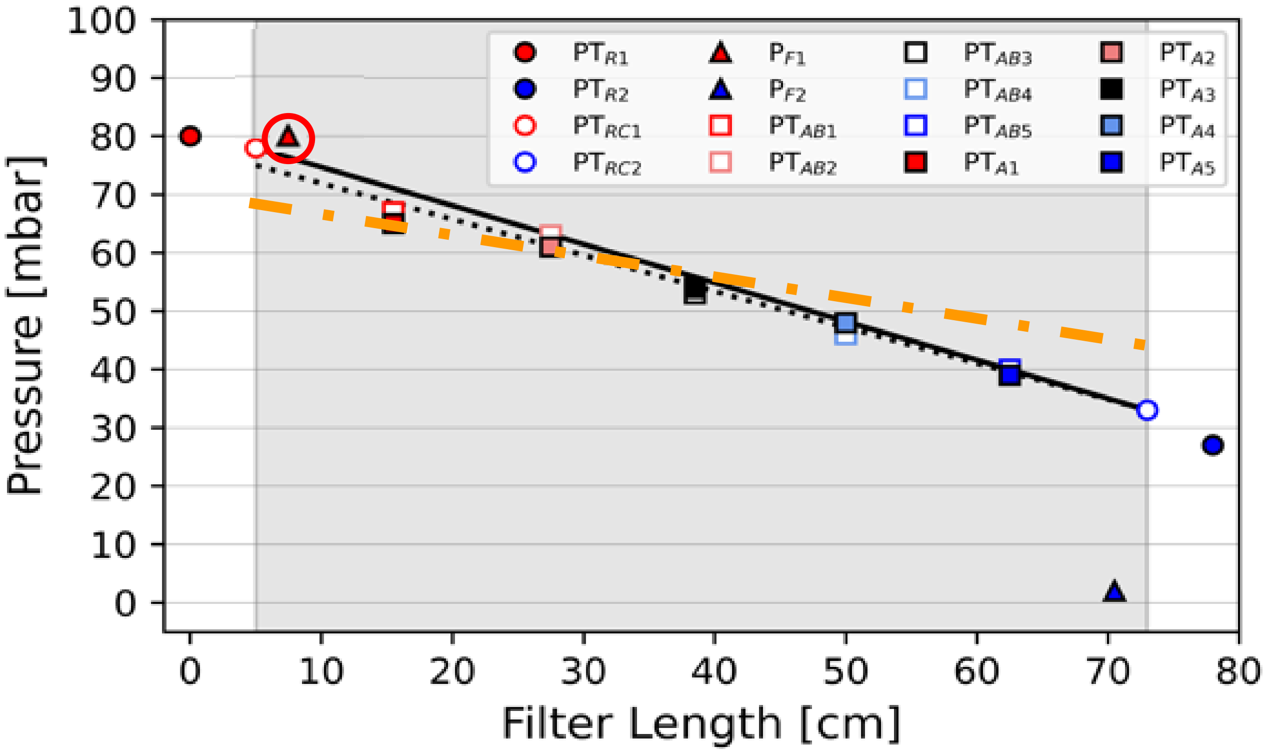
Delta Pressure Setpoint = 0 mbar



Modified from Ref[1]

→ Still starling flow…. inferior performance!

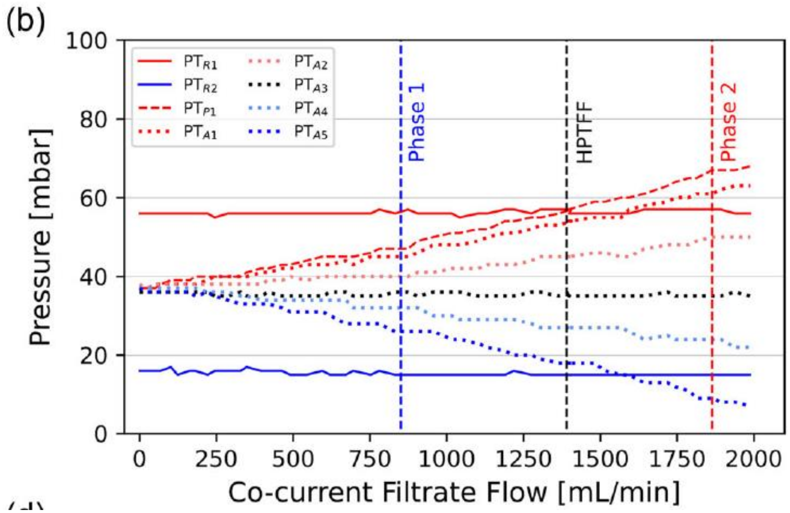
HPTFF Control Strategy: Delta Pressure

Better Pumps for Better Yield!

→ **Delta Pressure Setpoint must be determined! (water characterization)**

Characterization procedure:

- Set certain retentate flow (constant) and ramp the coflow.
- Then determine the optimal deltaP to achieve HPTFF based on PTA1-A5
- Repeat for various retentate flows
- Can be similarly applied for other filters than HF



Ref[1]

HPTFF Control Strategy: Delta Pressure

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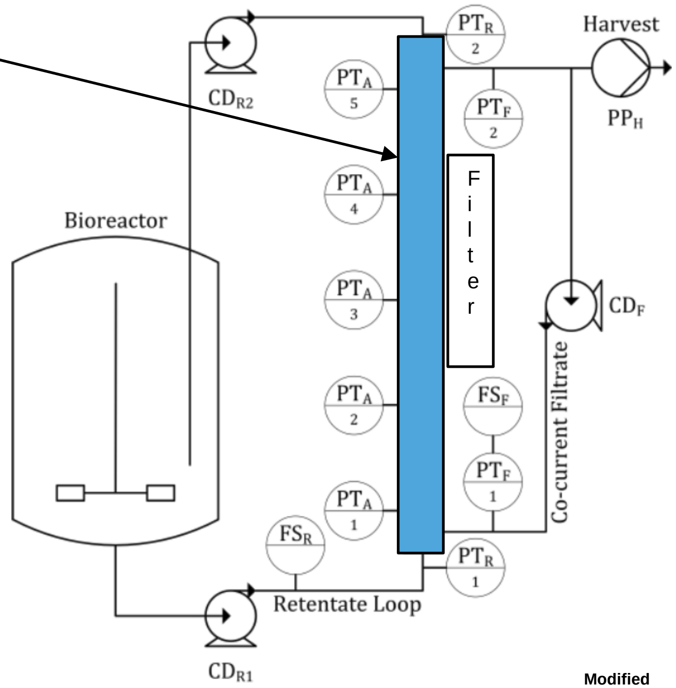
→ Contact us and we drill some holes

TFF Filter Characterization

Better Pumps for Better Yield!

1. **Filter shall be characterized prior to implementation of control strategy details.**
2. **Identification of Pressure profile along TFF membrane:**

Characterization Setup



Modified from Ref[1]

TFF Filter Characterization cont'd

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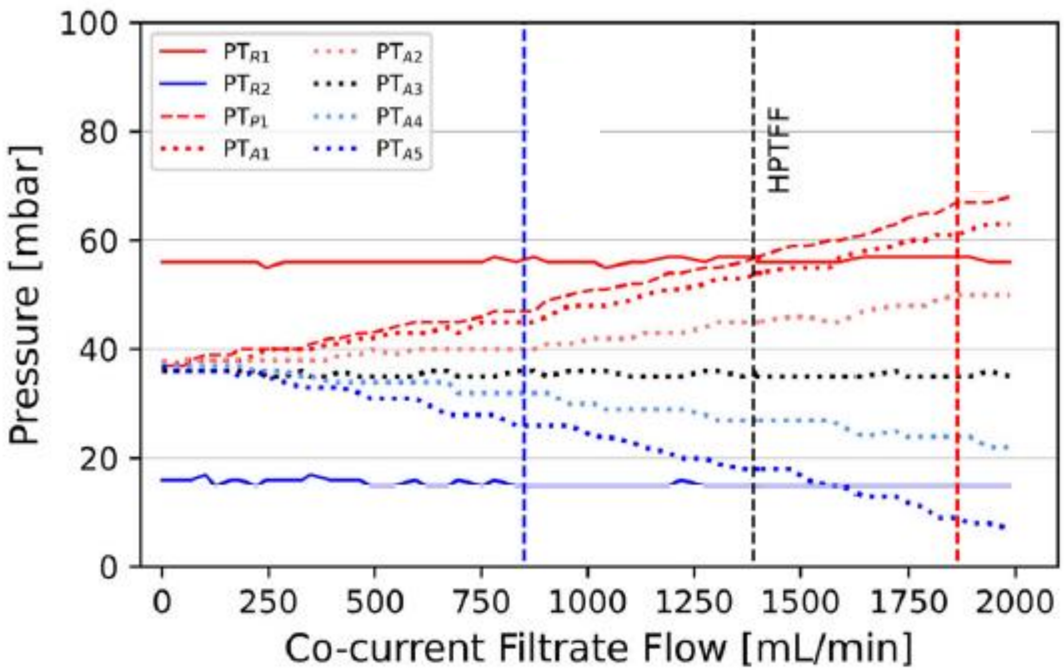
3. **Ramping Step: Keep retentate flow (crossflow) at constant process target and ramp the co-current filtrate flow from 0 to a large value definitely above HPTFF. Then identify the required coflow to achieve HPTFF by plotting the data depending on the filer length position (see 4.)**



Ref[1]

TFF Filter Characterization cont'd

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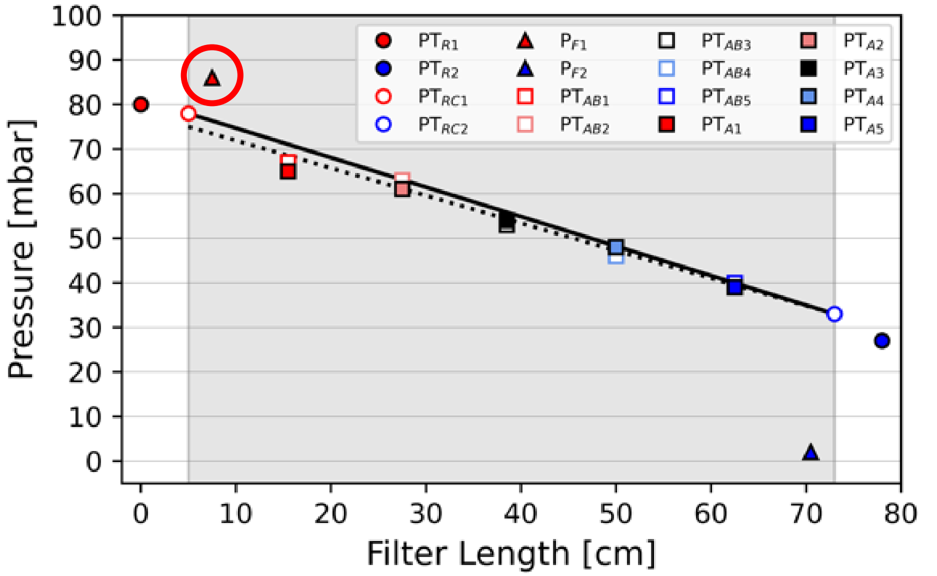
4. Set point of SETPOINT Delta Pressure determined by filter characterization:



Ref[1]

Can be zero, positive or negative delta P setpoint

-> determined by filter characterization

Co-Flow System Setup

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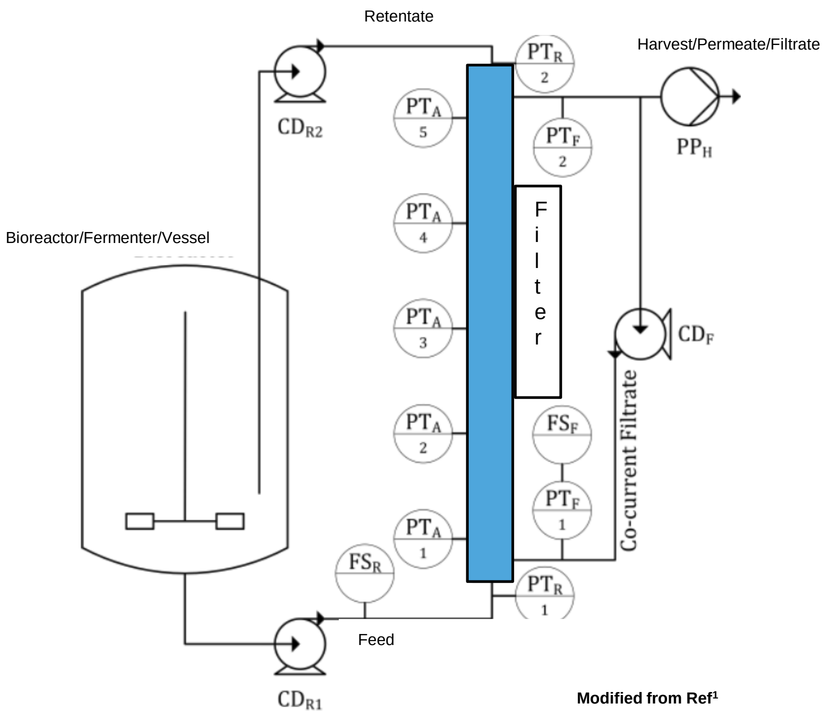
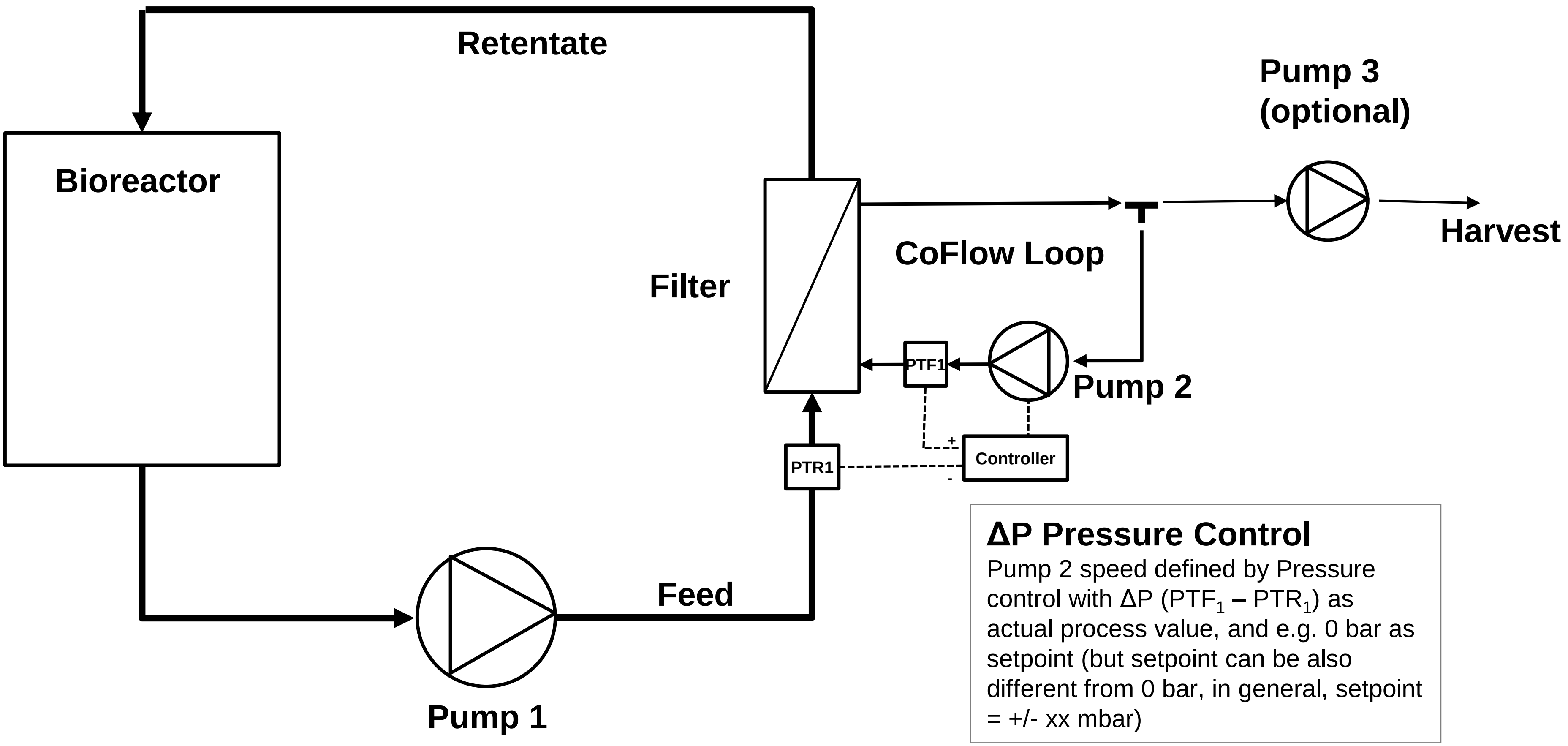


Modified from Ref[1]

- Setup can be applied to upstream and downstream processing. In downstream processing, vessel would not be a Bioreactor (for example, with mammalian cells) or Fermenter (for example, with microbial cells) but a vessel with product and/or buffer/liquid.
- PT_{R1}: Filter Feed Pressure can be measured prior filter or with integrated port as part of filter housing in feed entrance area of filter
- PT_{R2}: Filter Retentate Pressure can be measured after filter or with integrated port as part of filter housing in exit area of filter
- PT_{F1}: Permeate inlet pressure can be measured prior filter inlet
- PT_{F2}: Permeate outlet pressure can be measured after filter outlet
- PTA_x: Number of sensors along filter housing can be 5 (or more) or any different amount (min 1 sensor).

CoFlow System, Variant 1a

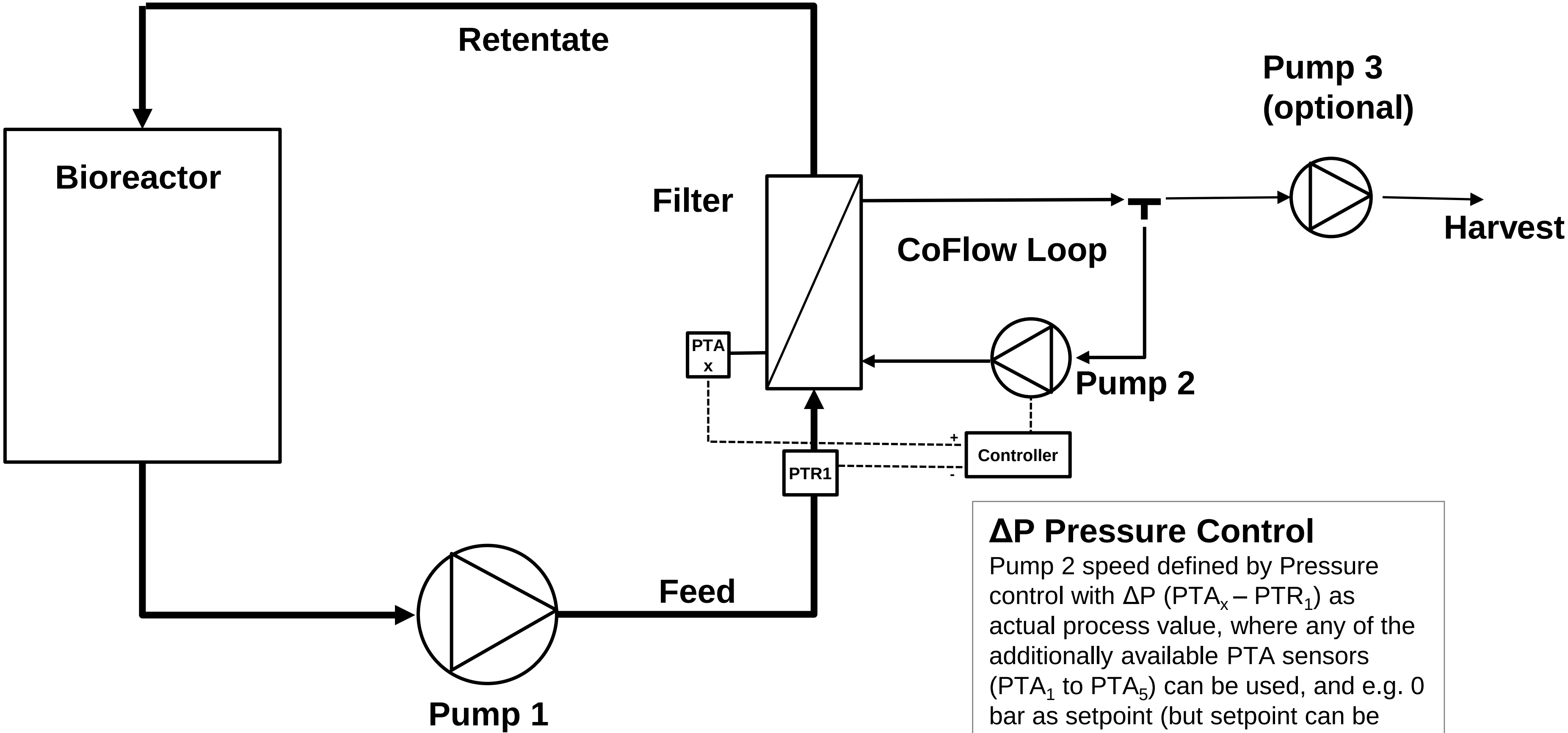
Better Pumps – Better Yield



ΔP Pressure Control
Pump 2 speed defined by Pressure control with ΔP (PTF_1 – PTR_1) as actual process value, and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

CoFlow System, Variant 1b

Better Pumps – Better Yield

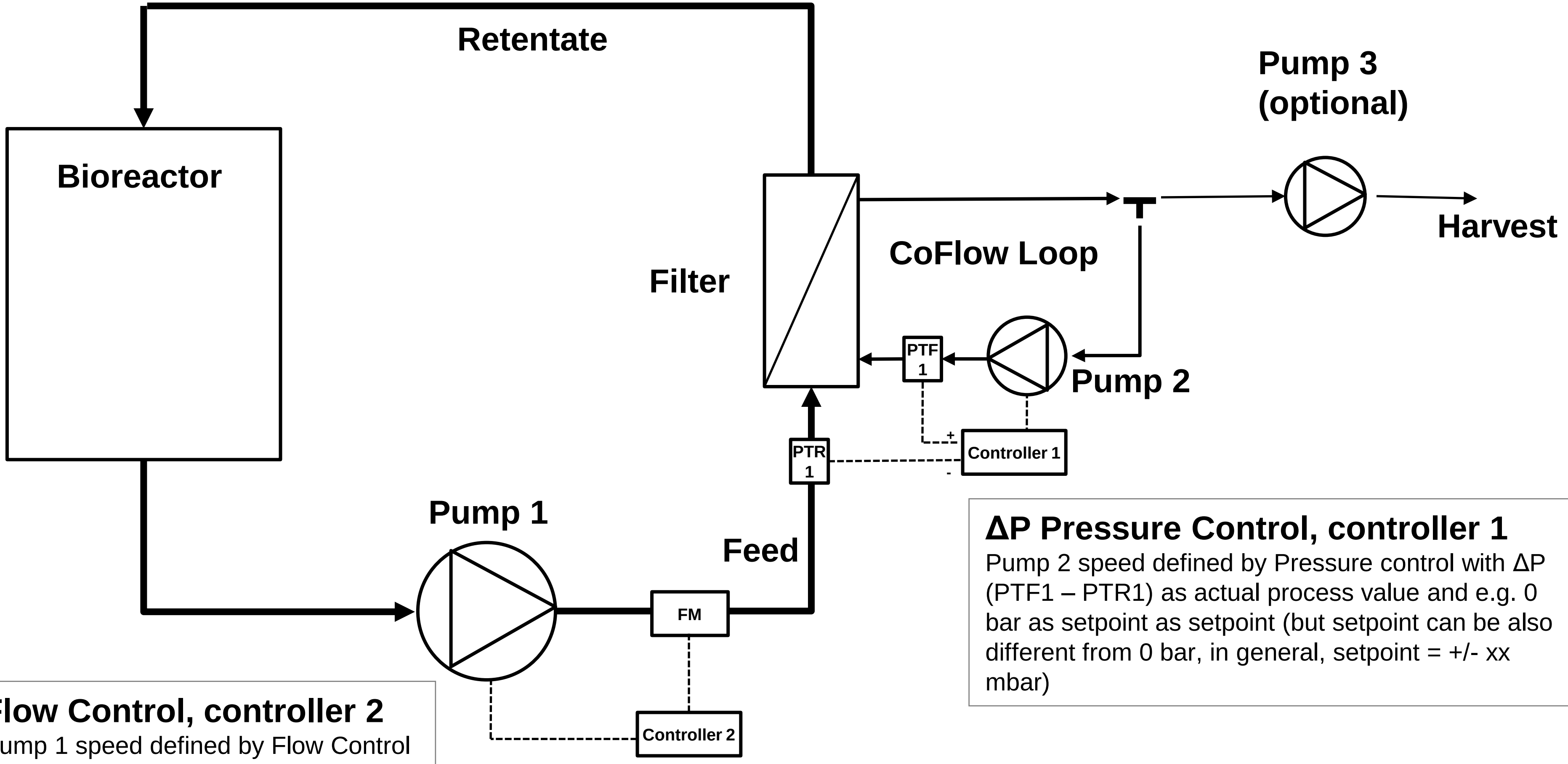


ΔP Pressure Control

Pump 2 speed defined by Pressure control with ΔP (PTA_x – PTR_1) as actual process value, where any of the additionally available PTA sensors (PTA_1 to PTA_5) can be used, and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

CoFlow System, Variant 2a

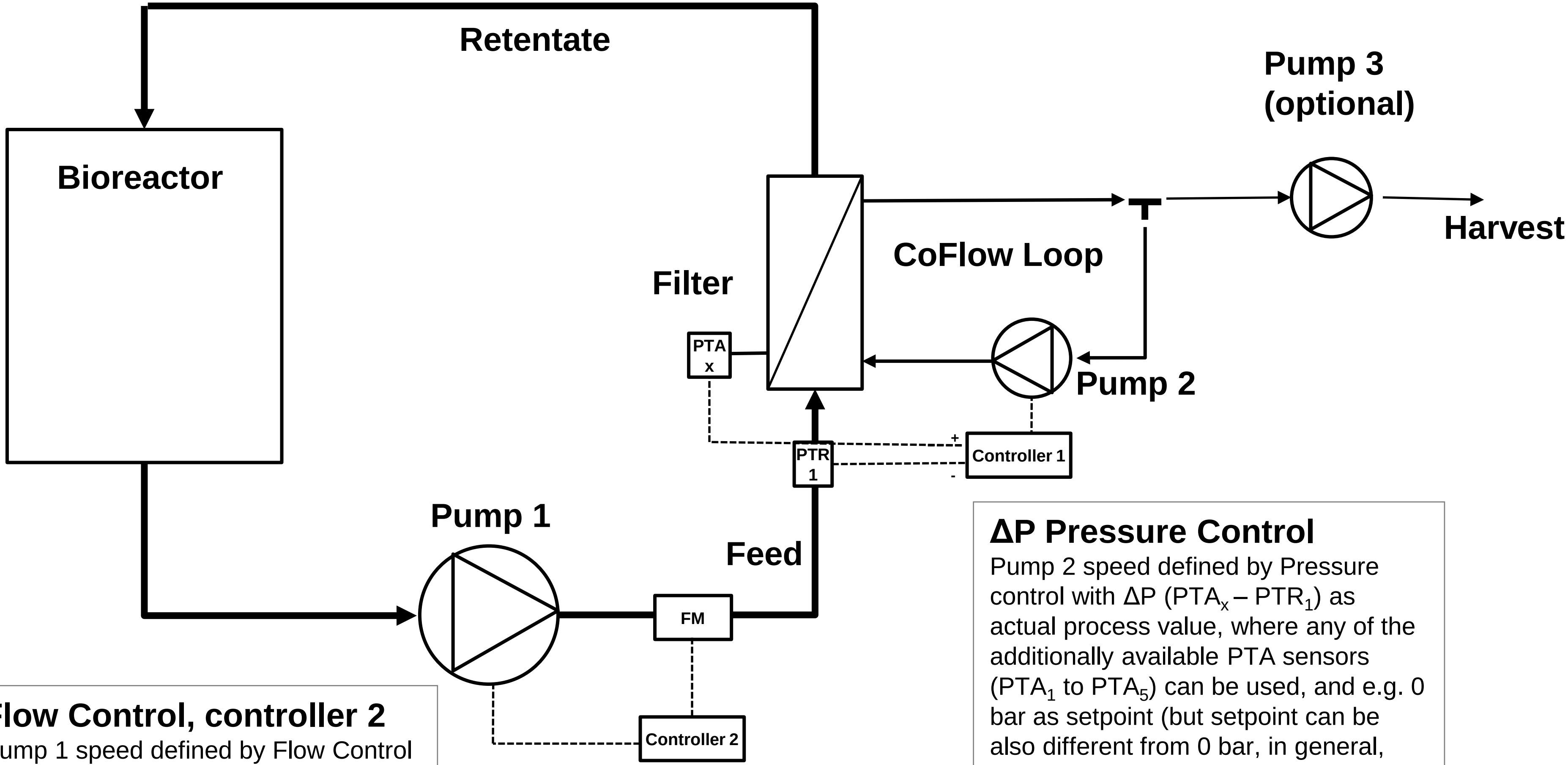
Better Pumps – Better Yield



ΔP Pressure Control, controller 1
Pump 2 speed defined by Pressure control with ΔP (PTF1 – PTR1) as actual process value and e.g. 0 bar as setpoint as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

Flow Control, controller 2
Pump 1 speed defined by Flow Control with FM as actual process value and required crossflow as setpoint

CoFlow System, Variant 2b



ΔP Pressure Control

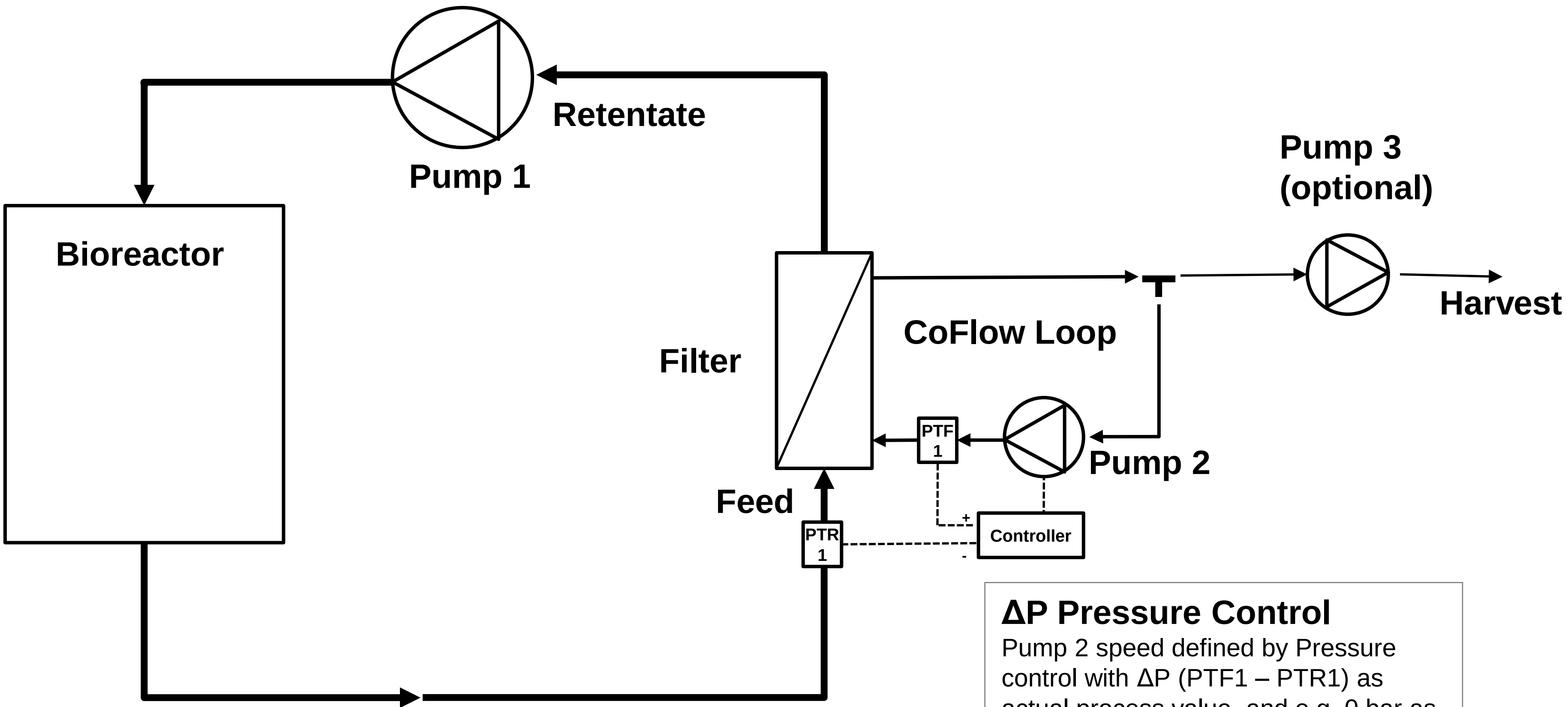
Pump 2 speed defined by Pressure control with ΔP ($PTA_x – PTR_1$) as actual process value, where any of the additionally available PTA sensors (PTA_1 to PTA_5) can be used, and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

Flow Control, controller 2

Pump 1 speed defined by Flow Control with FM as actual process value and required crossflow as setpoint

CoFlow System, Variant 3a

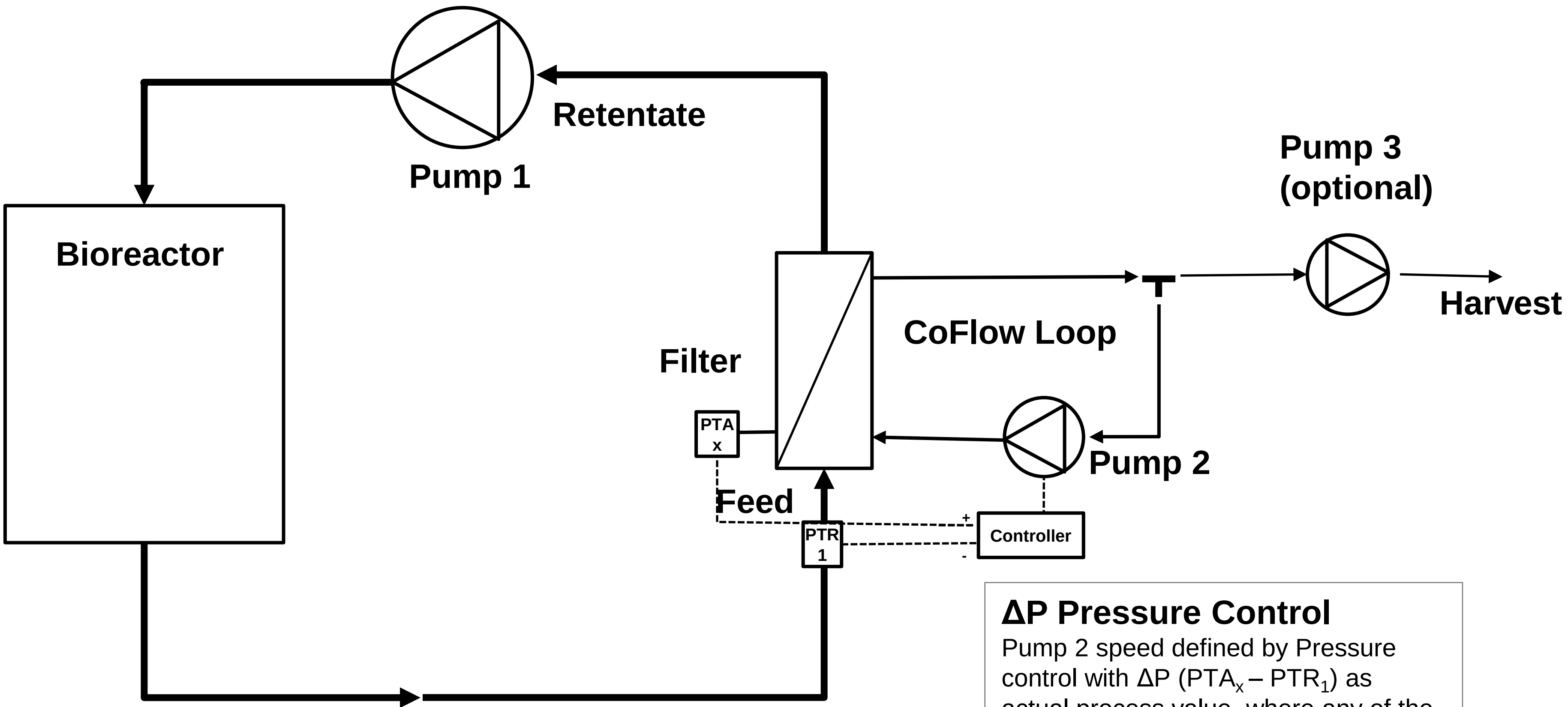
Better Pumps – Better Yield



ΔP Pressure Control
Pump 2 speed defined by Pressure control with ΔP (PTF1 – PTR1) as actual process value, and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

CoFlow System, Variant 3b

Better Pumps – Better Yield

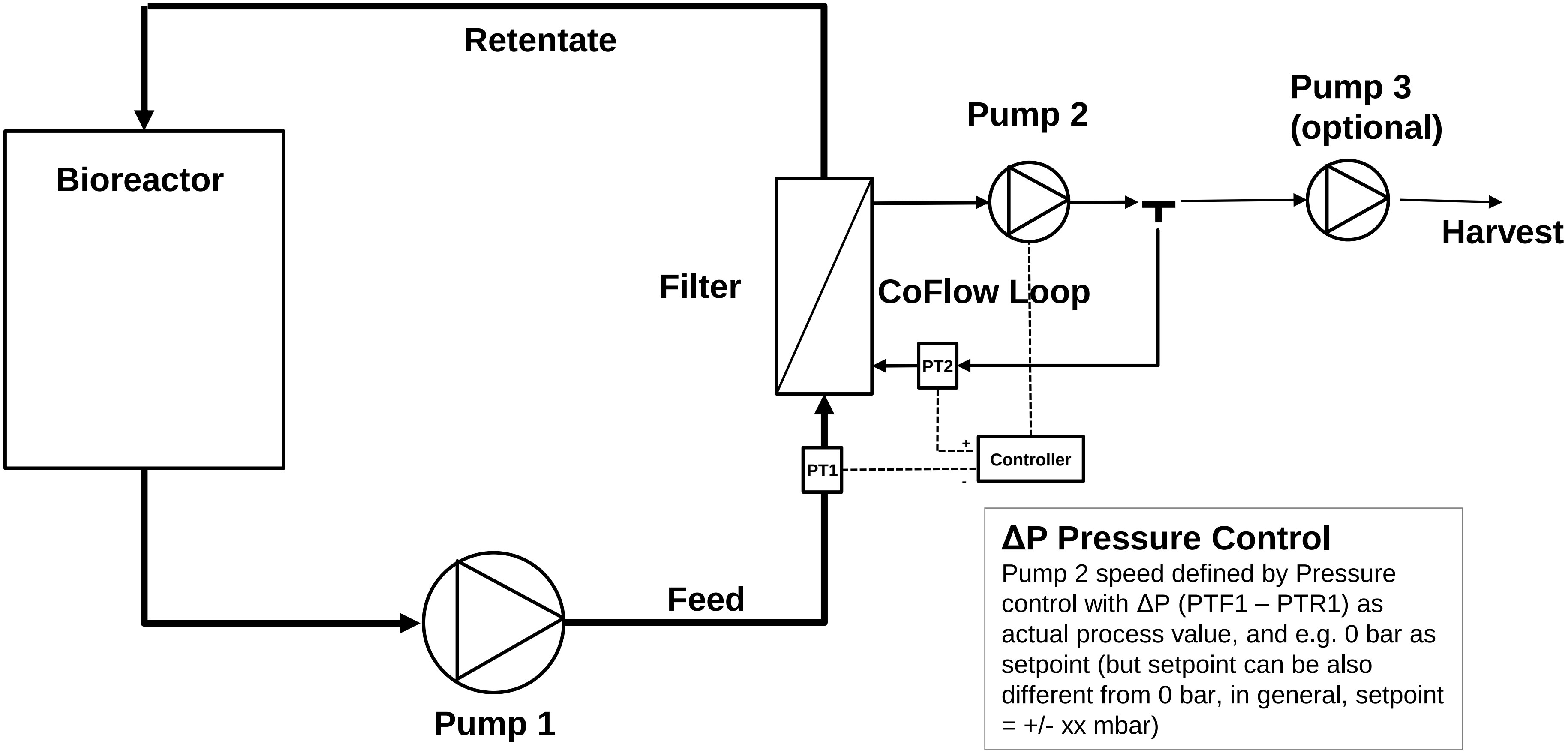


ΔP Pressure Control

Pump 2 speed defined by Pressure control with ΔP (PTA_x – PTR_1) as actual process value, where any of the additionally available PTA sensors (PTA_1 to PTA_5) can be used, and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

CoFlow System, Variant 4a

Better Pumps – Better Yield

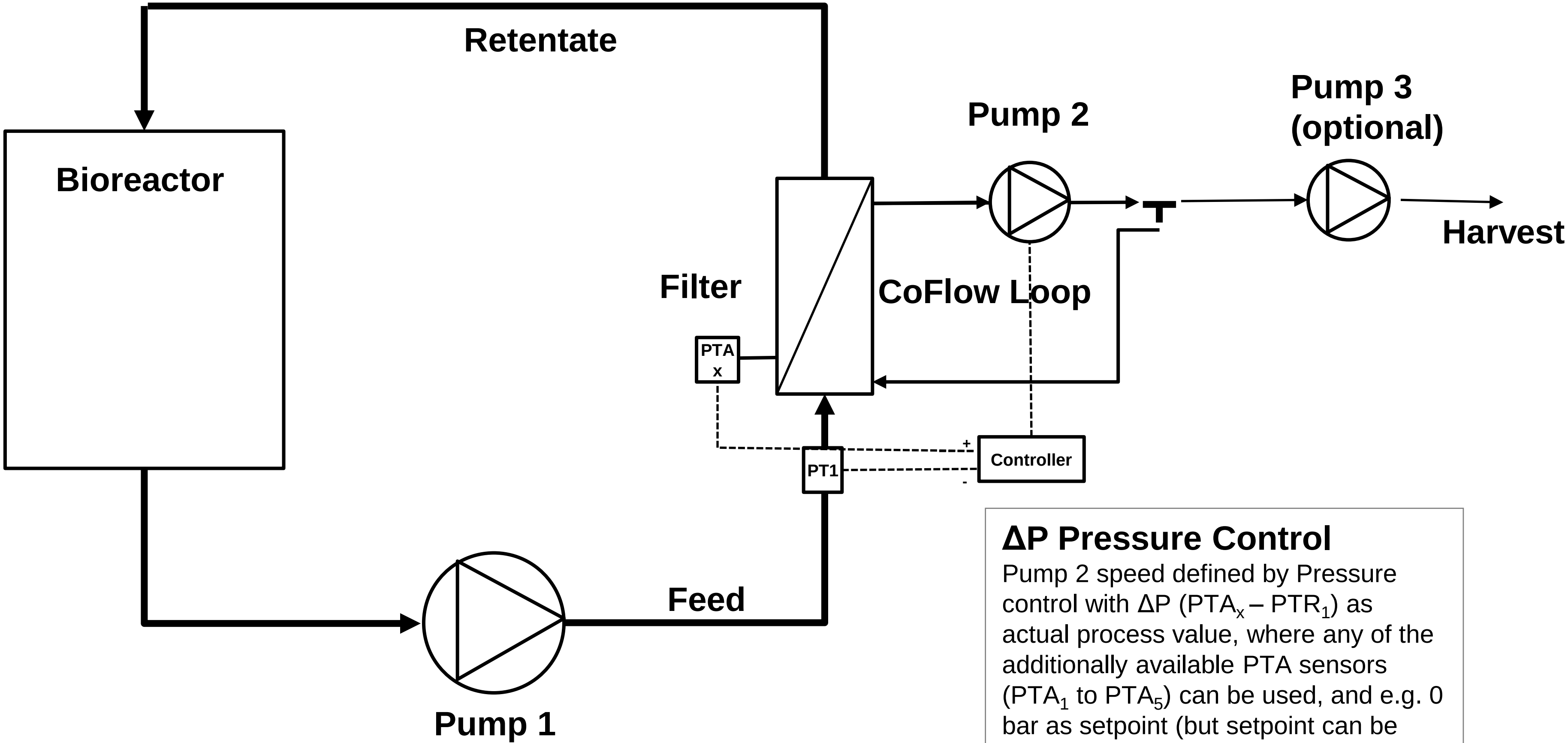


ΔP Pressure Control

Pump 2 speed defined by Pressure control with ΔP (PTF1 – PTR1) as actual process value, and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

CoFlow System, Variant 4b

Better Pumps – Better Yield

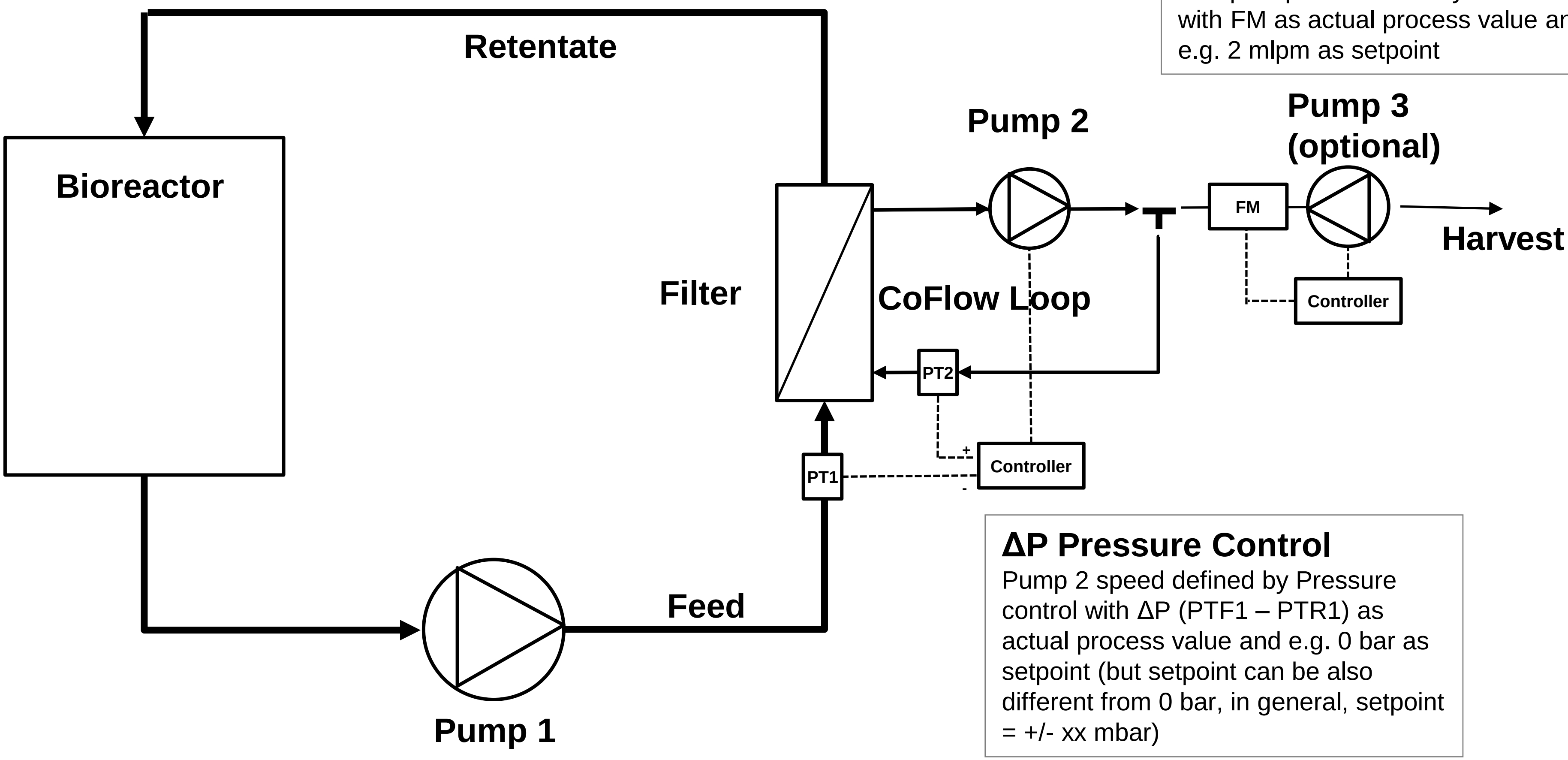


ΔP Pressure Control

Pump 2 speed defined by Pressure control with ΔP (PTA_x – PTR_1) as actual process value, where any of the additionally available PTA sensors (PTA_1 to PTA_5) can be used, and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

CoFlow System, Variant 5a

Better Pumps – Better Yield

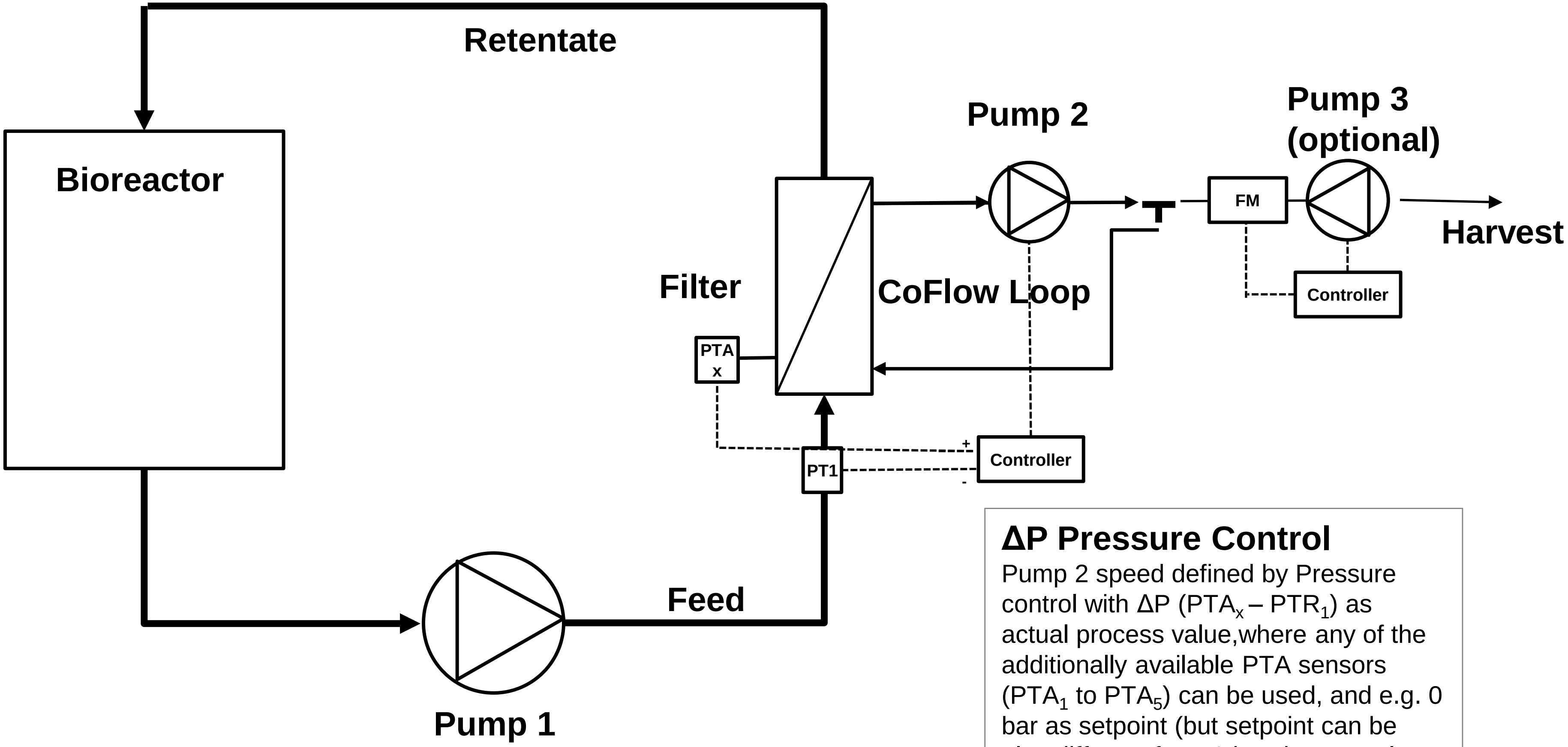


Reverse Flow Control
Pump 3 speed defined by Flow Control with FM as actual process value and e.g. 2 mlpm as setpoint

ΔP Pressure Control
Pump 2 speed defined by Pressure control with ΔP (PTF1 – PTR1) as actual process value and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

CoFlow System, Variant 5b

Better Pumps – Better Yield

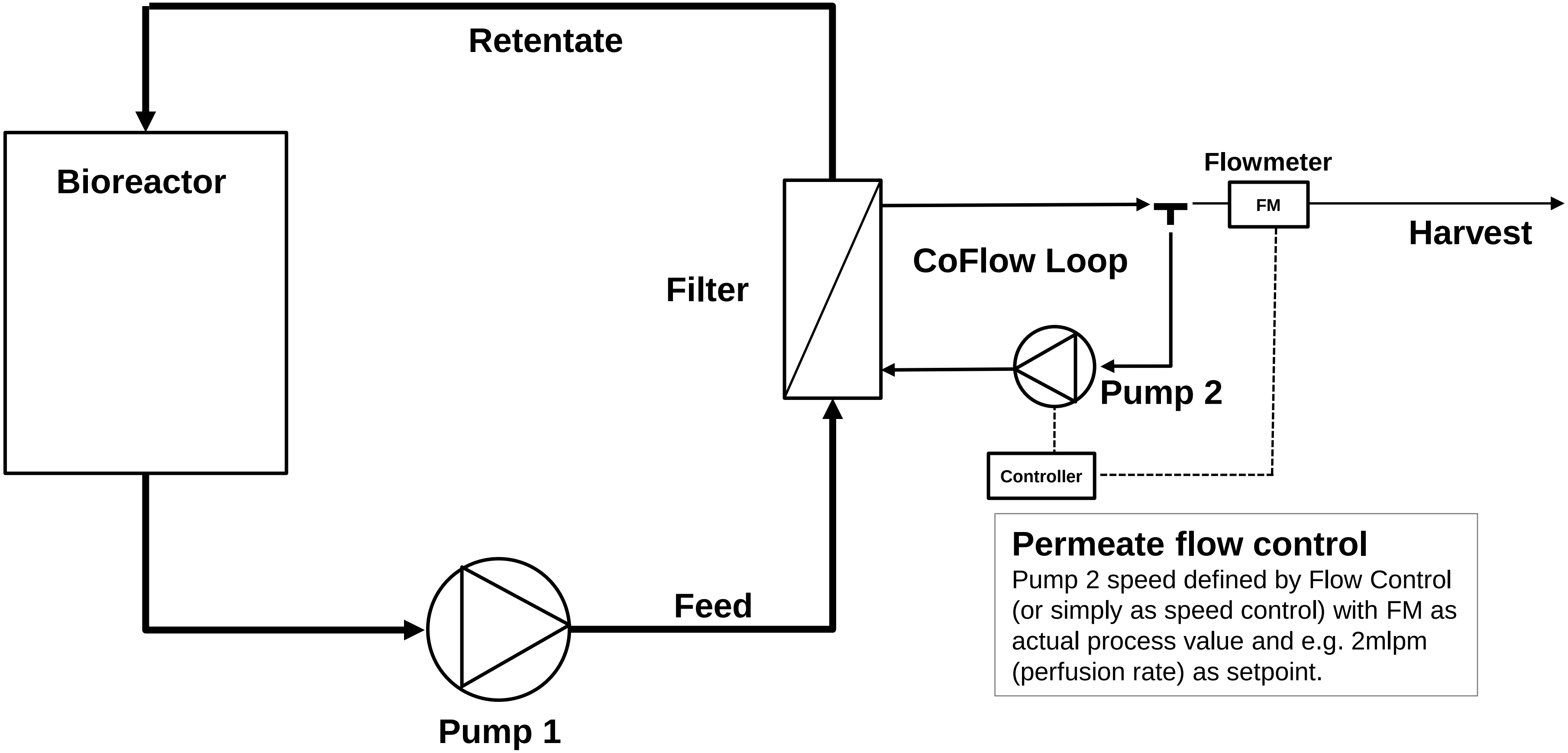


Reverse Flow Control
Pump 3 speed defined by Flow Control with FM as actual process value and e.g. 2 mlpm as setpoint

ΔP Pressure Control
Pump 2 speed defined by Pressure control with ΔP (PTA_x – PTR_1) as actual process value,where any of the additionally available PTA sensors (PTA_1 to PTA_5) can be used, and e.g. 0 bar as setpoint (but setpoint can be also different from 0 bar, in general, setpoint = +/- xx mbar)

CoFlow System, Variant 6

Better Pumps – Better Yield

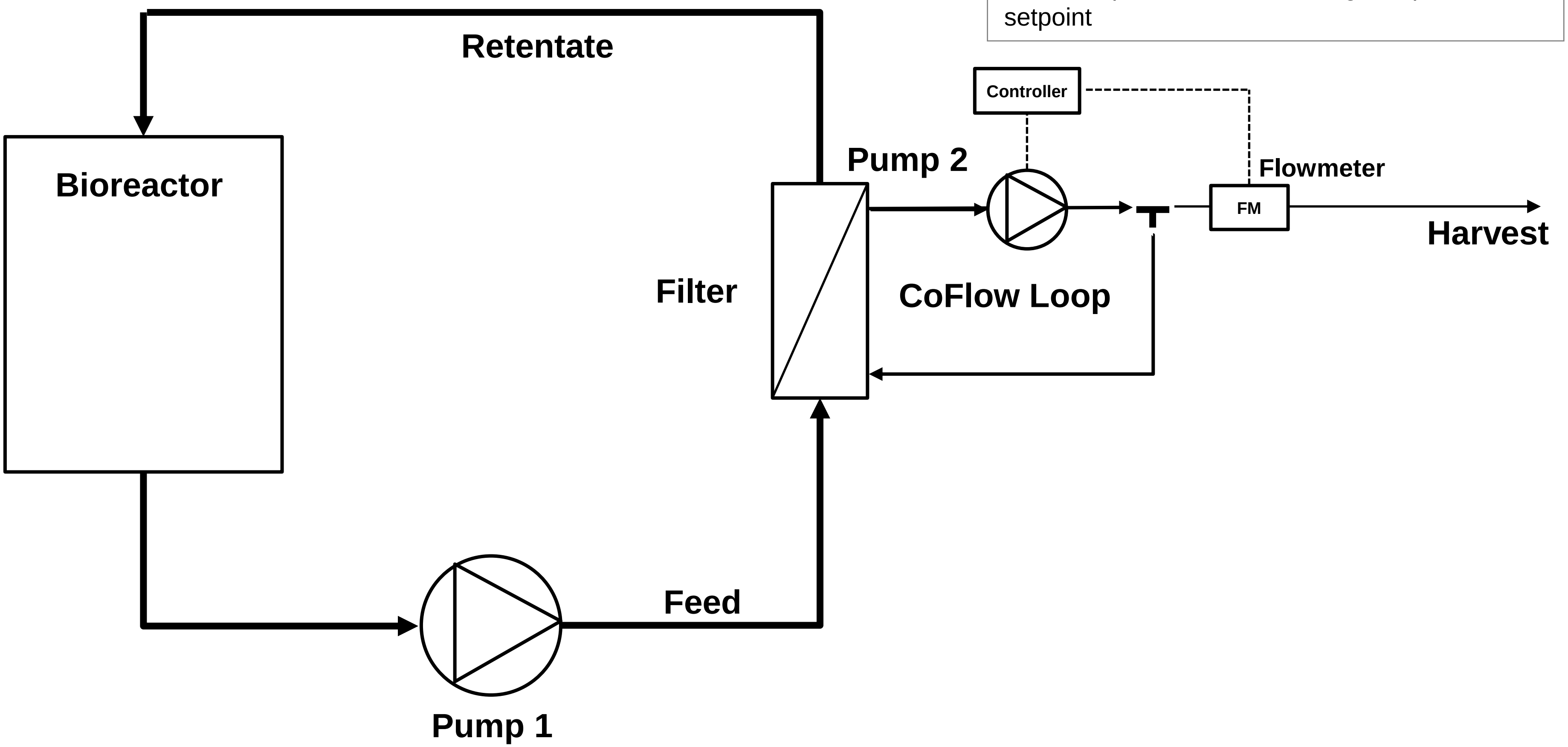


Permeate flow control

Pump 2 speed defined by Flow Control (or simply as speed control) with FM as actual process value and e.g. 2mlpm (perfusion rate) as setpoint.

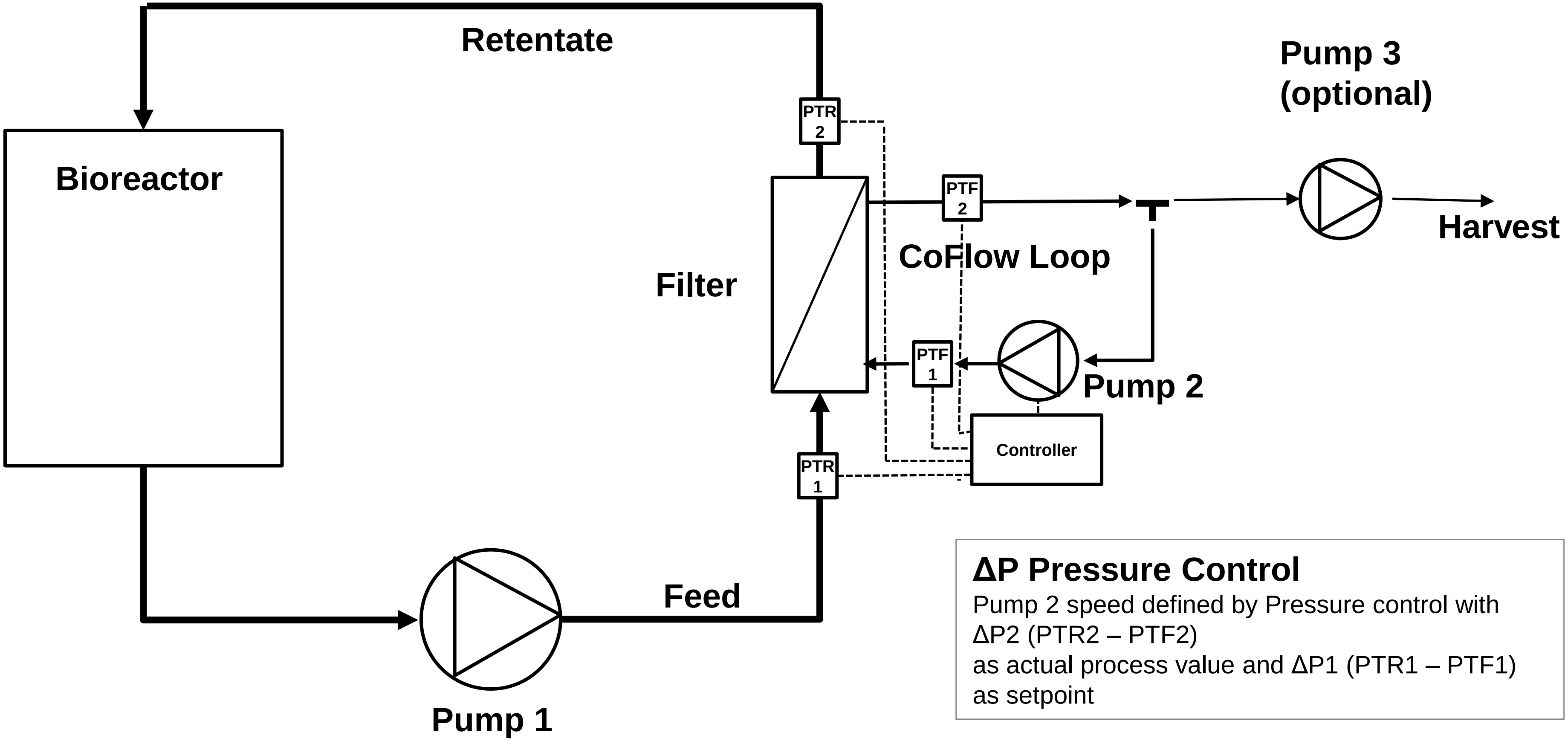
CoFlow System, Variant 7

Harvest Permeate flow control
Pump 2 speed defined by Flow Control with FM as actual process value and e.g. 2mlpm as setpoint



CoFlow System, Variant 8a

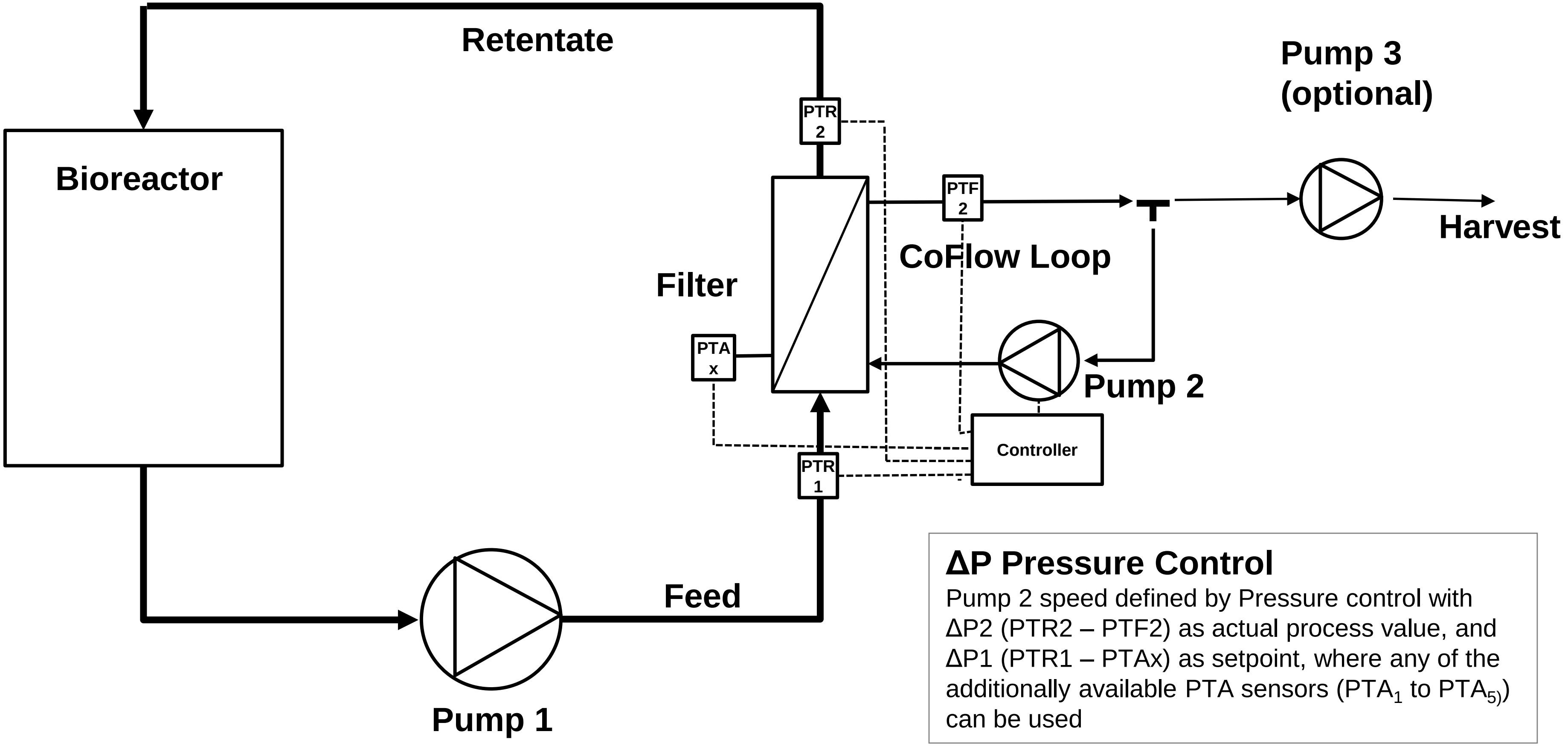
Better Pumps – Better Yield



ΔP Pressure Control
Pump 2 speed defined by Pressure control with ΔP2 (PTR2 – PTF2)
as actual process value and ΔP1 (PTR1 – PTF1) as setpoint

CoFlow System, Variant 8b

Better Pumps – Better Yield

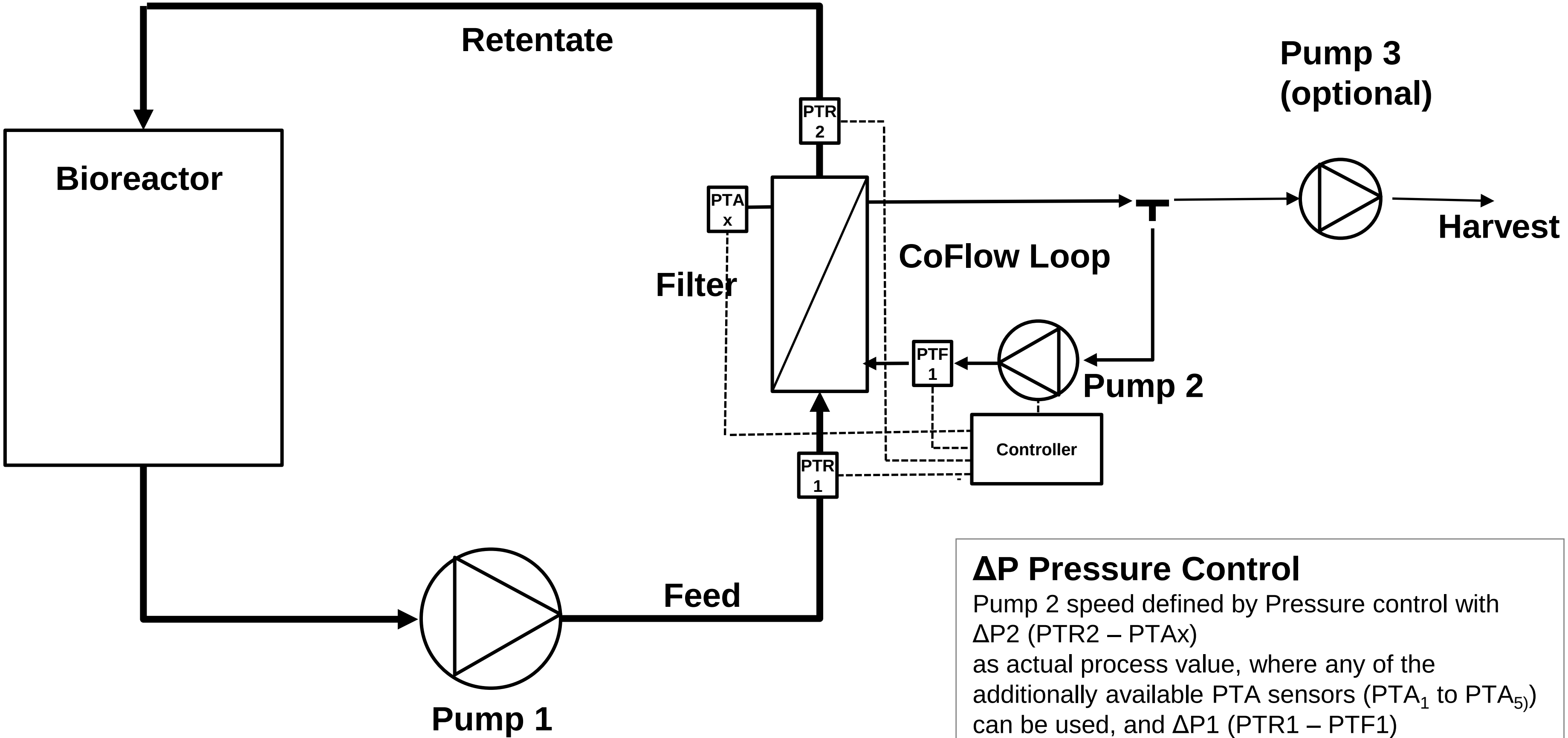


ΔP Pressure Control

Pump 2 speed defined by Pressure control with ΔP2 (PTR2 – PTF2) as actual process value, and ΔP1 (PTR1 – PTAx) as setpoint, where any of the additionally available PTA sensors (PTA_1 to $PTA_{5)}$) can be used

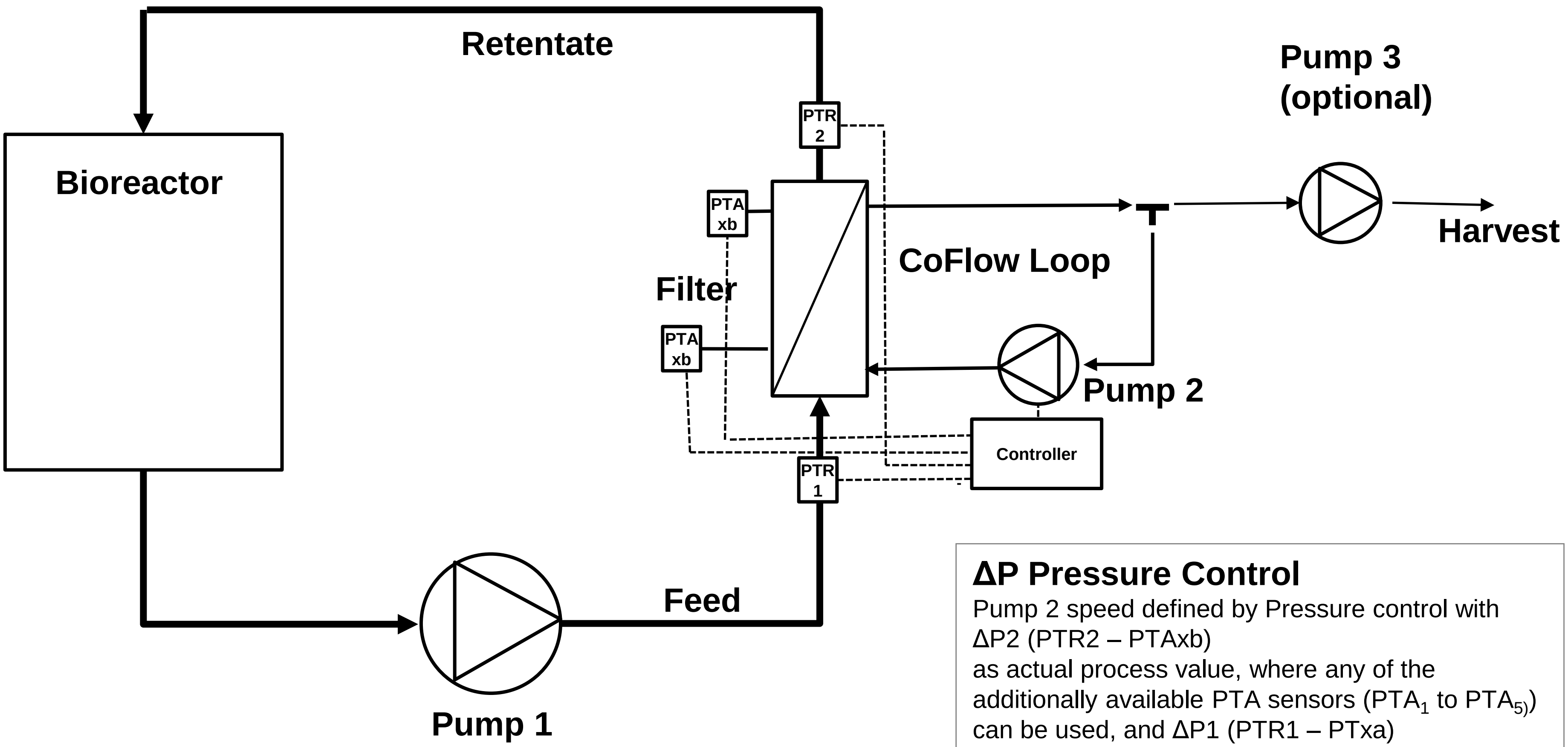
CoFlow System, Variant 8c

Better Pumps – Better Yield



ΔP Pressure Control
Pump 2 speed defined by Pressure control with
ΔP2 (PTR2 – PTAx)
as actual process value, where any of the additionally available PTA sensors (PTA_1 to PTA_5)) can be used, and ΔP1 (PTR1 – PTF1)
as setpoint

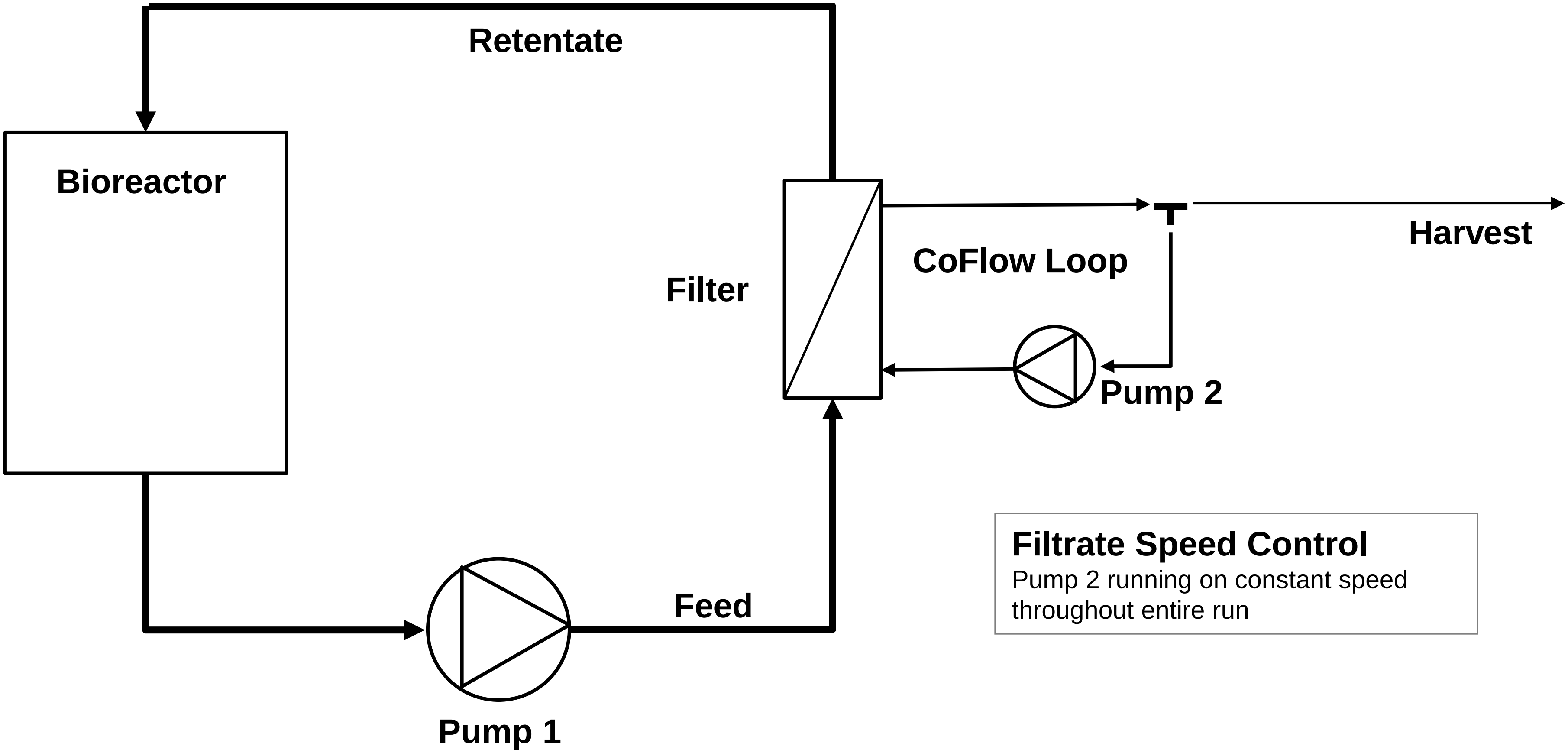
CoFlow System, Variant 8d



ΔP Pressure Control
Pump 2 speed defined by Pressure control with ΔP2 (PTR2 – PTAxb) as actual process value, where any of the additionally available PTA sensors (PTA_1 to $PTA_{5)}$) can be used, and ΔP1 (PTR1 – PTxa) as setpoint, where any of the additionally available PTA sensors (PTA_1 to $PTA_{5)}$) can be used

CoFlow System, Variant 9

Better Pumps – Better Yield

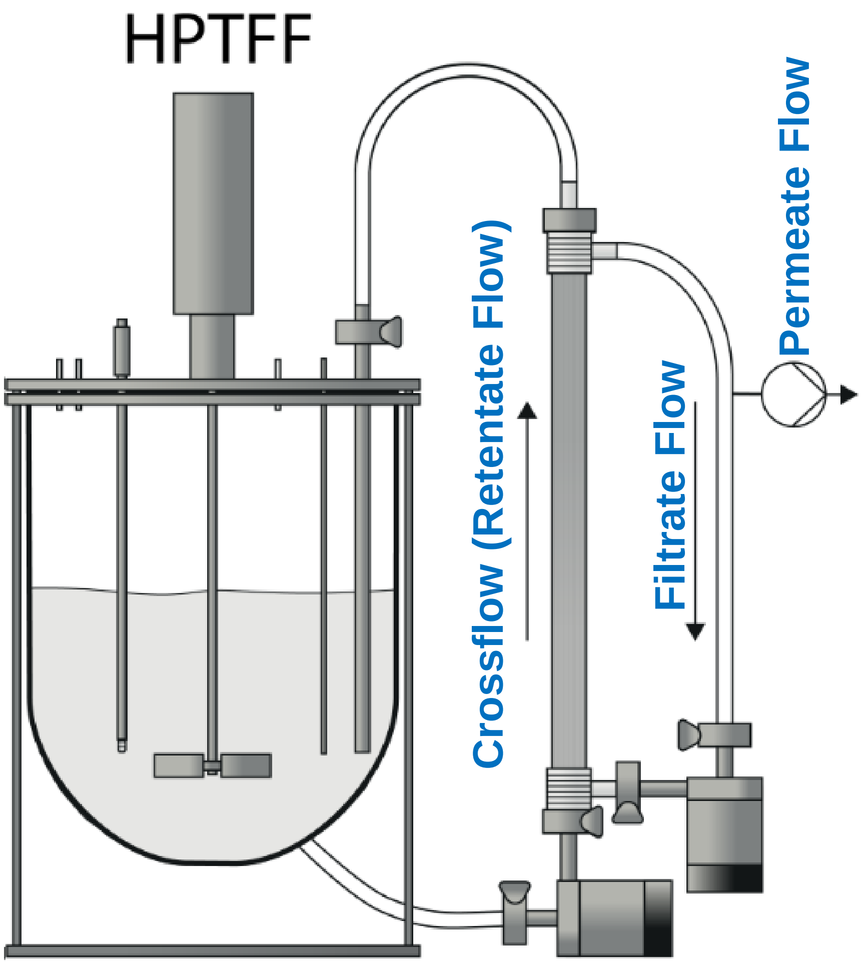


Filtrate Speed Control
Pump 2 running on constant speed throughout entire run

Crossflow vs. Co-current Filtrate Flow

Better Pumps for Better Yield!

FAQ: How high is the co-current Filtrate Flow ?



Depends on many factors:

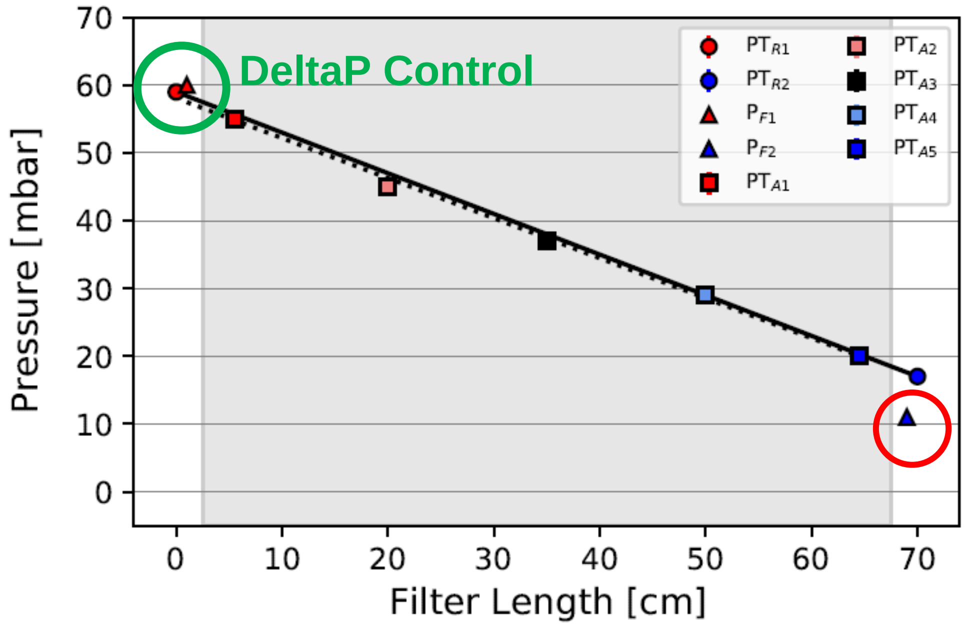
- Culture Viscosity
- Operating Conditions (Crossflow)
- Filter Characteristics

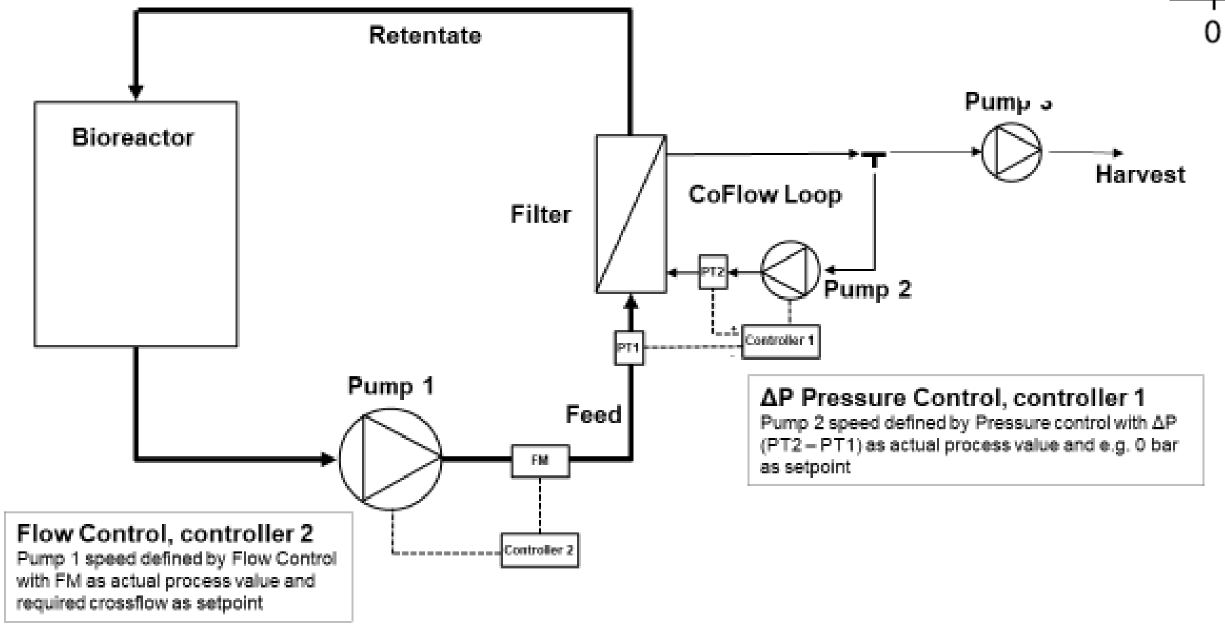
Slope Control Strategy vs. DeltaP Control

Alternative Control Strategy: Slope Control

Better Pumps for Better Yield!

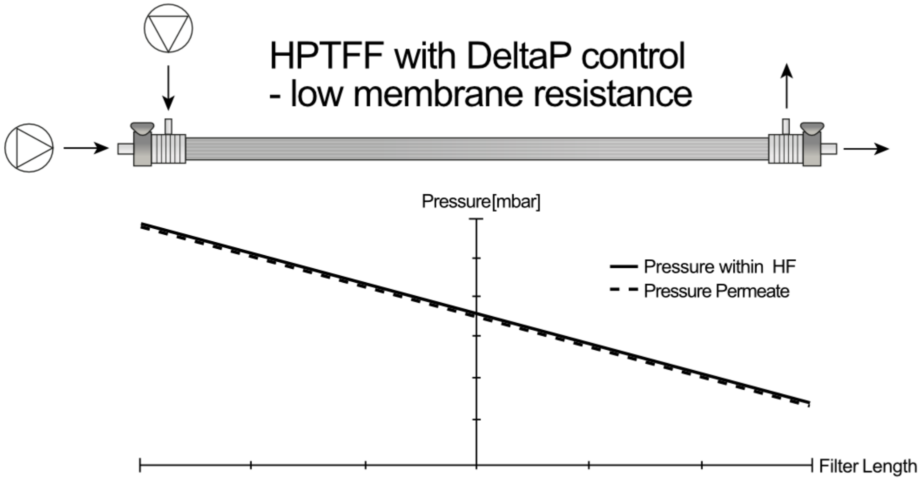
- DeltaP: Match PTR1 (inlet of crossflow loop) and PF1 (inlet of co-flow loop)

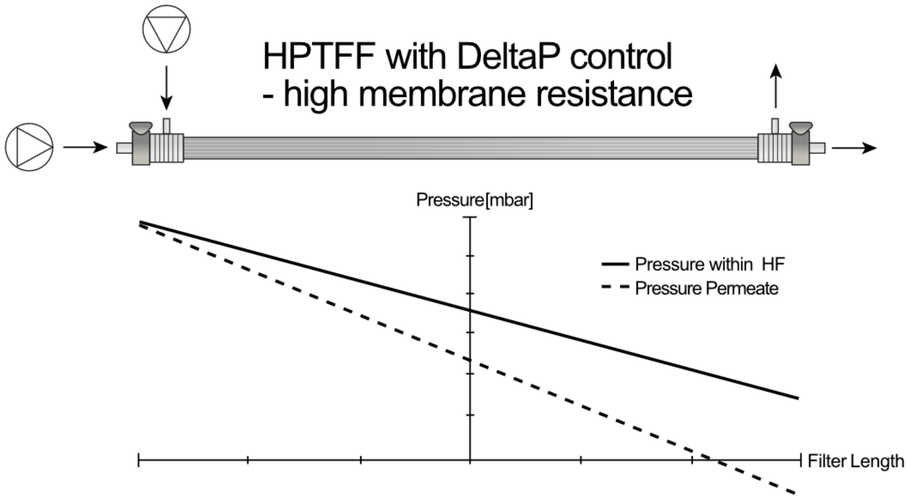




DeltaP Control Strategy: Limitations

Better Pumps for Better Yield!





Low membrane resistance:

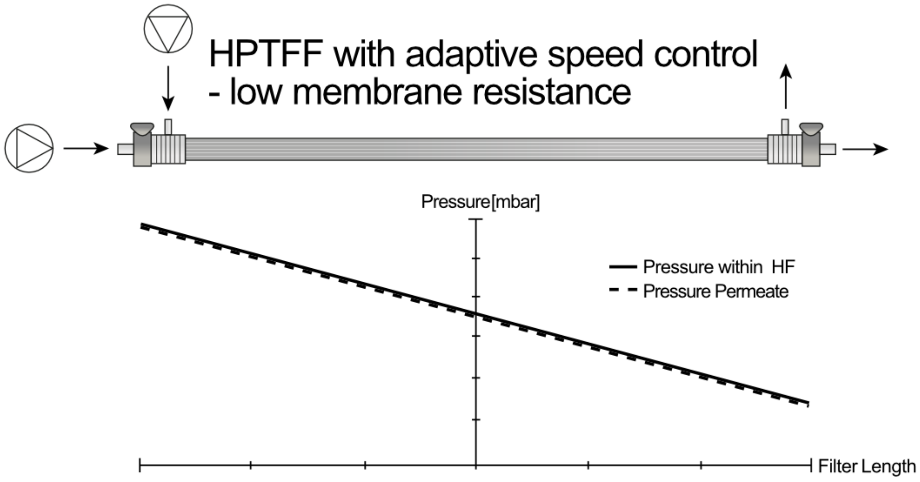
- Uniform TMP

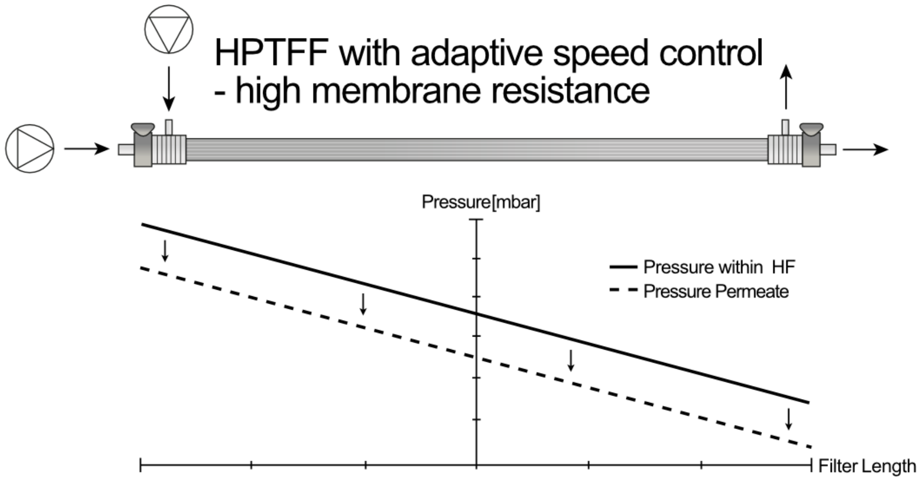
High membrane resistance (filter fouling):

- Non-uniform TMP
- High co-flow for DeltaP control

Slope Control: Concept

Better Pumps for Better Yield!





Low membrane resistance:

- Uniform TMP

High membrane resistance (filter fouling):

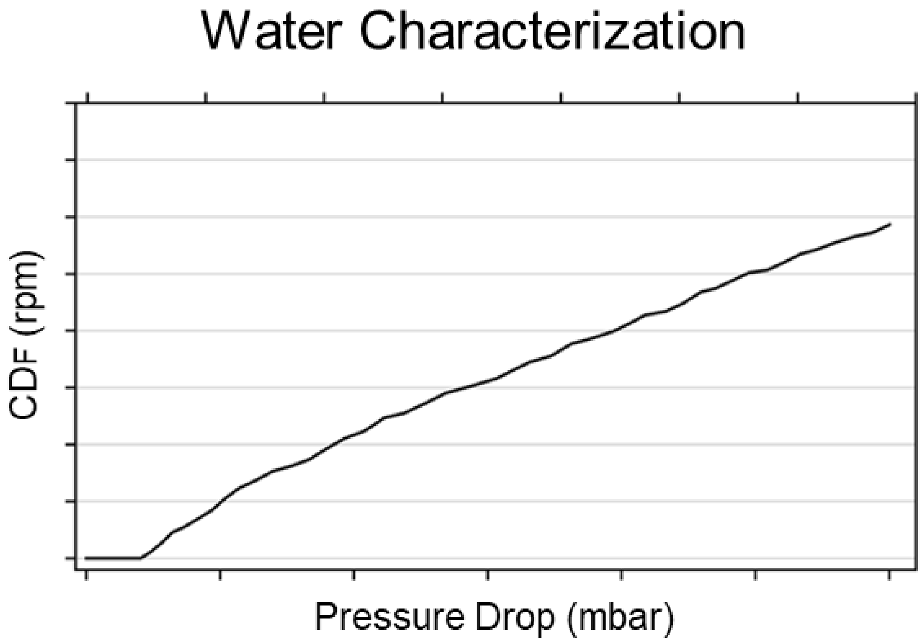
- **Uniform** TMP
- Initial co-flow for DeltaP control

Slope Control: Setup

Better Pumps for Better Yield!

Requirements:

- Assumption: constant viscosity in permeate
- Filter characterization (Pressure Drop vs. Filtrate flow (or rpm))
- Pressure sensors to measure Pressure Drop (PT_{R1} and PT_{R2})
- Adaptive Speed control (Adjustment of rpm of CD_F)

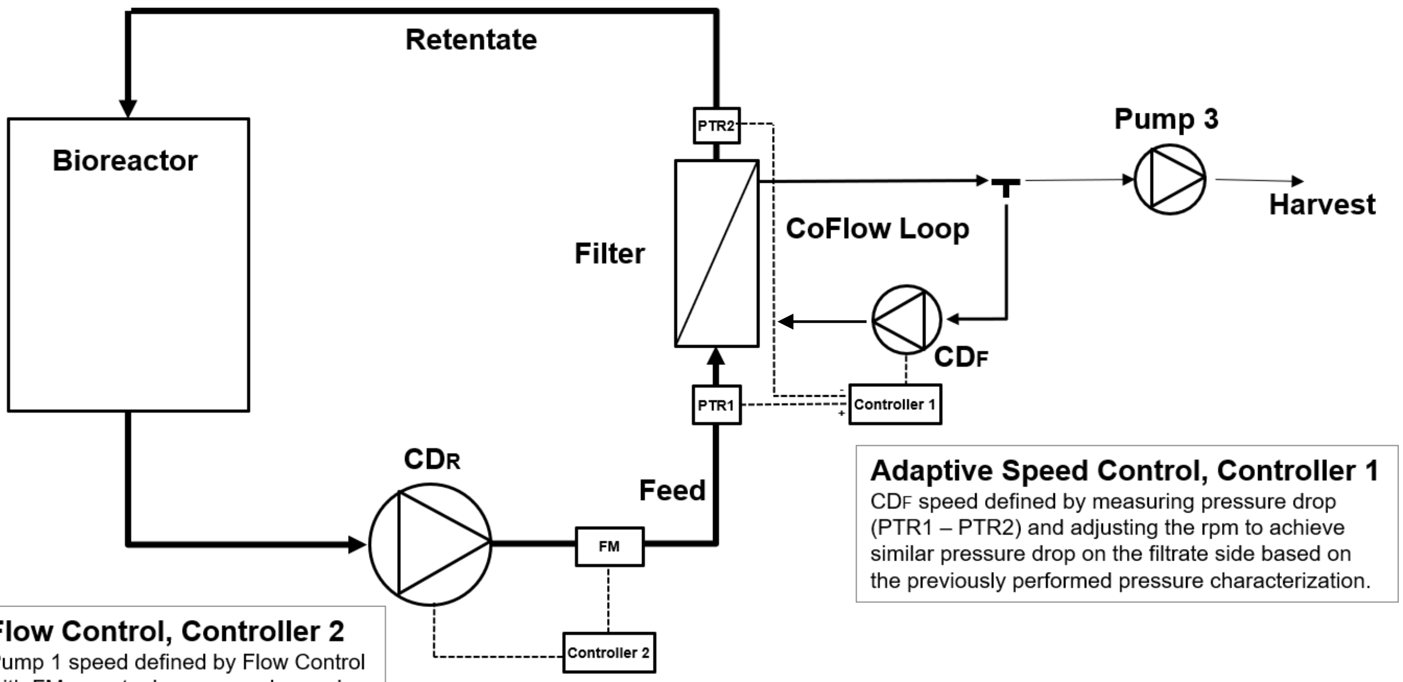


Slope Control: Setup

Better Pumps for Better Yield!

Advantages:

- No issues with pressure sensor readings as observed in co-flow loop
- Uniform TMP also when fouling starts
- Better performance when filter fouling occurs
- In the simples form, just set a flow control based on the characterization in both the retentate loop and a separate flow or speed control in the coflow loop



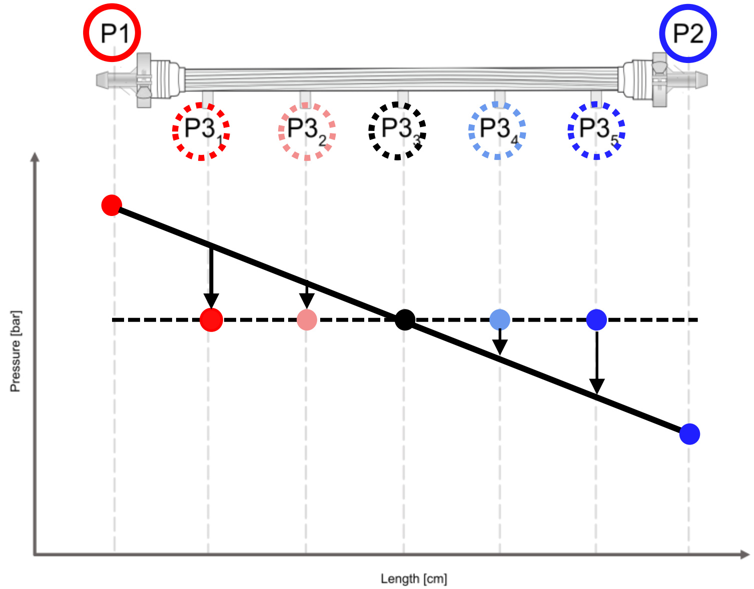
Adaptive Speed Control, Controller 1
CDF speed defined by measuring pressure drop (PTR1 – PTR2) and adjusting the rpm to achieve similar pressure drop on the filtrate side based on the previously performed pressure characterization.

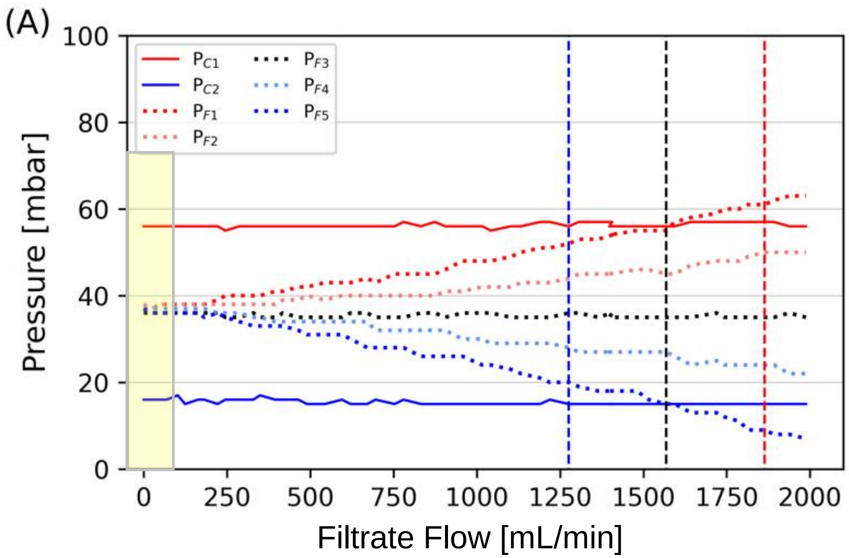
Flow Control, Controller 2
Pump 1 speed defined by Flow Control with FM as actual process value and required crossflow as setpoint
Alternative: Simple speed control

Co-current Filtrate Flow

Stepping co-current TFF (scTFF)

Stepping co-current TFF





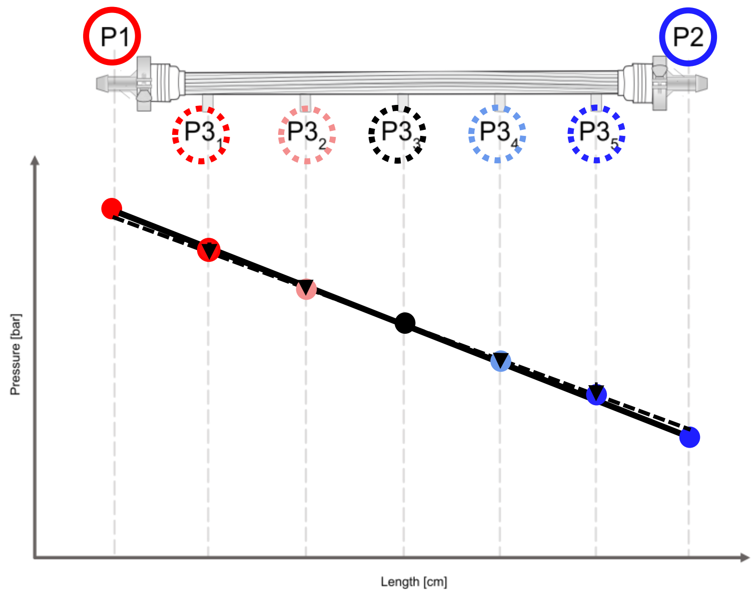
Ref[1]

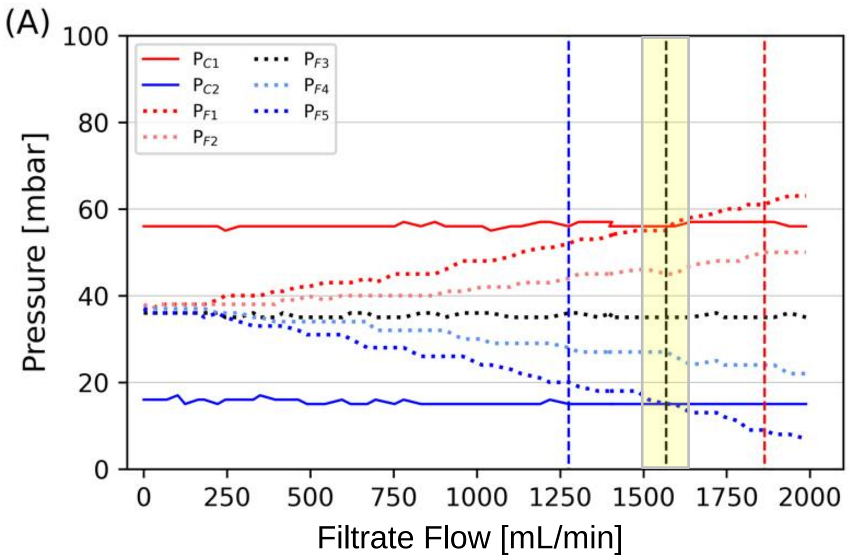
Standard TFF:

- No co-current filtrate flow

Stepping co-current TFF

Better Pumps for Better Yield!



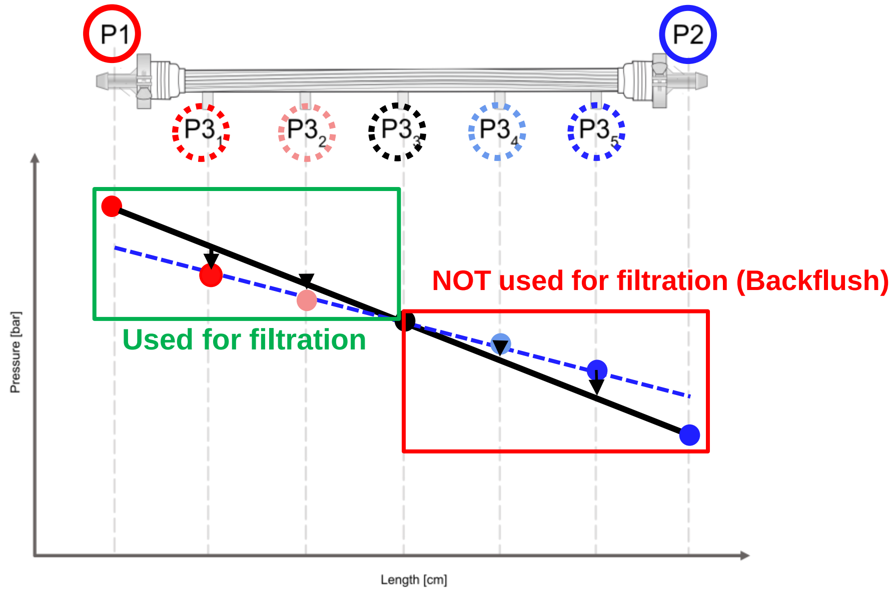


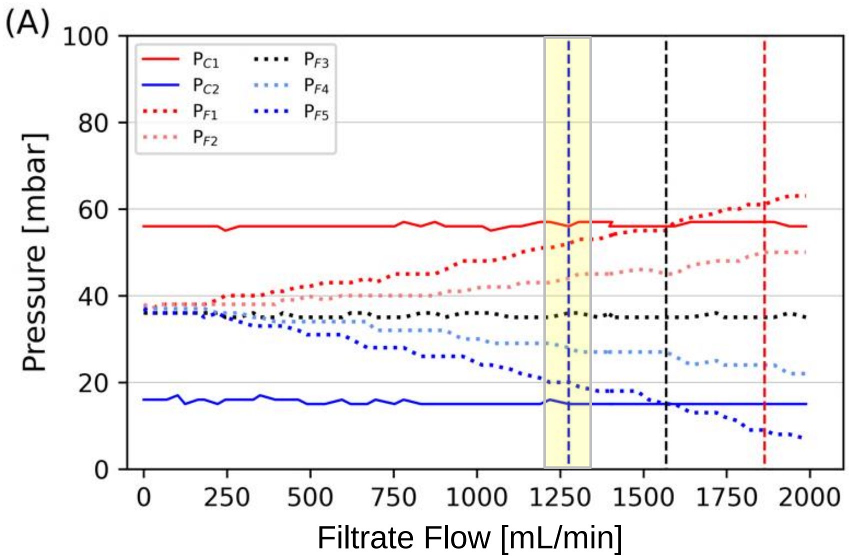
Ref[1]

HPTFF:

- Co-current filtrate flow to match P1 and P3
- No TMP along fibers (almost)

Stepping co-current TFF





Ref[1]

scTFF (Phase 1):

- Coflow < HPTFF Coflow
- Backflush 2nd half of filter

Stepping co-current TFF

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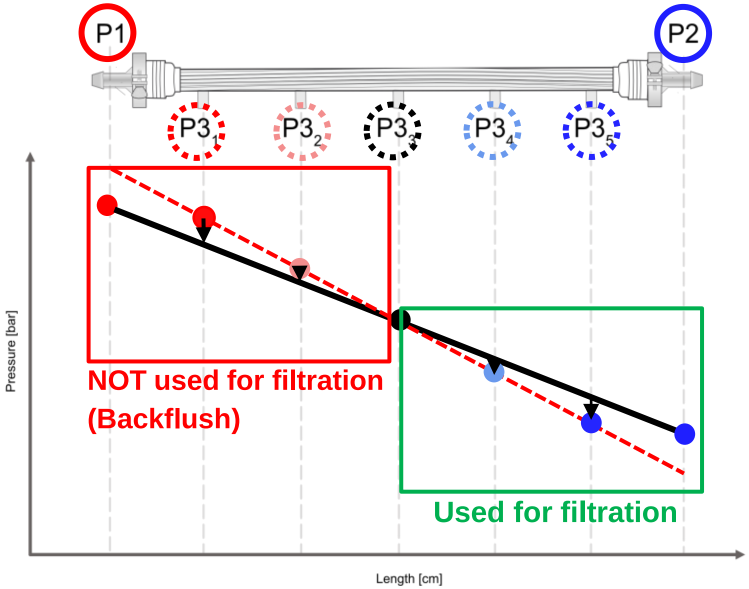
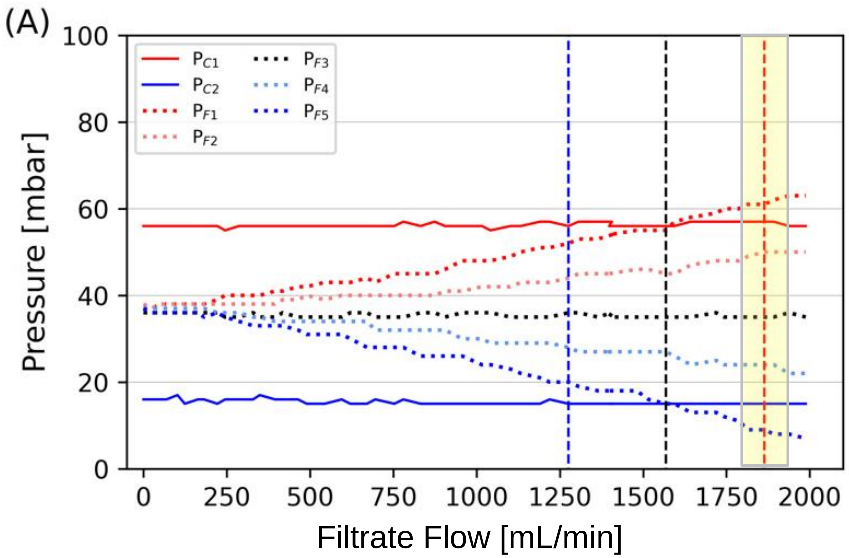
Better Pumps for Better Yield!



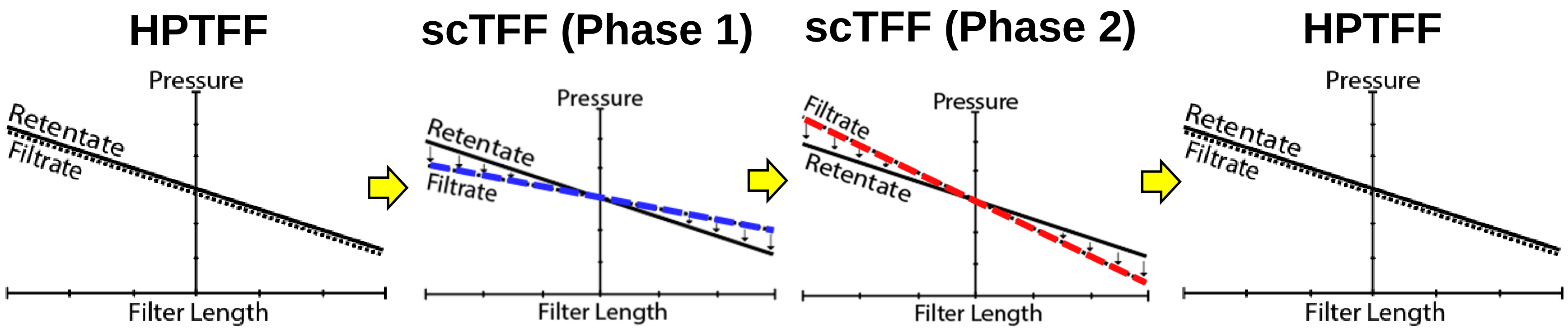


Ref[1]

scTFF (Phase 2):

- Coflow > HPTFF Coflow
- Backflush 1st half of filter

Strategies for scTFF



Idea 1: Continuous scTFF

- Switch from scTFF phase 1 directly to scTFF Phase2
- Similar system to ATF but with tunable Bachflush

Idea 2: HPTFF with alternating Backflush

- Mostly HPTFF operation
- To sweep, change from HPTFF to scTFF P1 and then P2, before going back to HPTFF
- Frequency completely flexible

→ The better version of ATF?

Reference

Ref[1]

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ARTICLE

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Co-current filtrate flow in TFF perfusion processes: Decoupling transmembrane pressure from crossflow to improve product sieving

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Abstract

Hollow fiber-based membrane filtration has emerged as the dominant technology for cell retention in perfusion processes yet significant challenges in alleviating filter fouling remain unsolved. In this work, the benefits of co-current filtrate flow applied to a tangential flow filtration (TFF) module to reduce or even completely remove Starling recirculation caused by the axial pressure drop within the module was studied by pressure characterization experiments and perfusion cell culture runs. Additionally, a novel concept to achieve alternating Starling flow within unidirectional TFF was investigated. Pressure profiles demonstrated that precise flow control can be achieved with both lab-scale and manufacturing-scale filters. TFF systems with co-current flow showed up to 40% higher product sieving compared to standard TFF. The decoupling of transmembrane pressure from crossflow velocity and filter characteristics in co-current TFF alleviates common challenges for hollow fiber-

rTFF Strategies

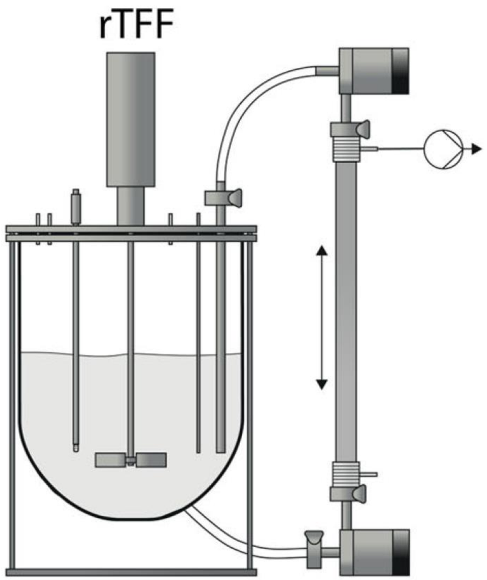
System Setup and Control Strategy

rTFF Setup Possibilities

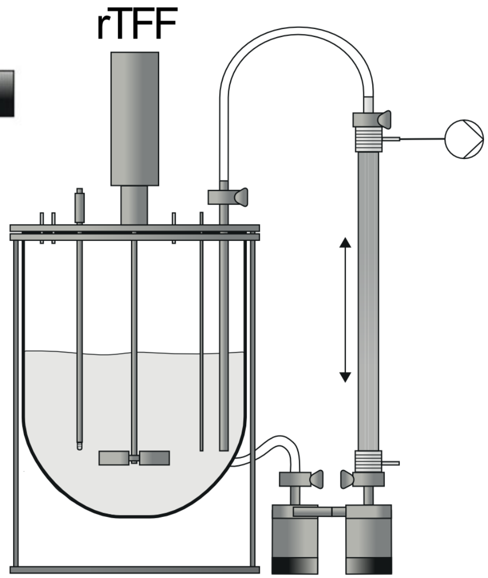
Better Pumps for Better Yield!

Setup:

- rTFF can be set up by placing 2 pumps inversely into the retentate loop.
- **Push-push:** both pumps push the liquid through the filter in an alternating manner (both pump outlets face to filter module)
- **Pull-pull:** both pumps pull the liquid out of the filter in an alternating manner (both pump inlets face to filter module)
- **Push-pull:** One pump pushes the liquid through filter and one pump pulls liquid out of filter (pump inlet of first pump facing to filter, pump outlet from other pump facing to filter) (Also pull –push arangement possible.



Push - Push



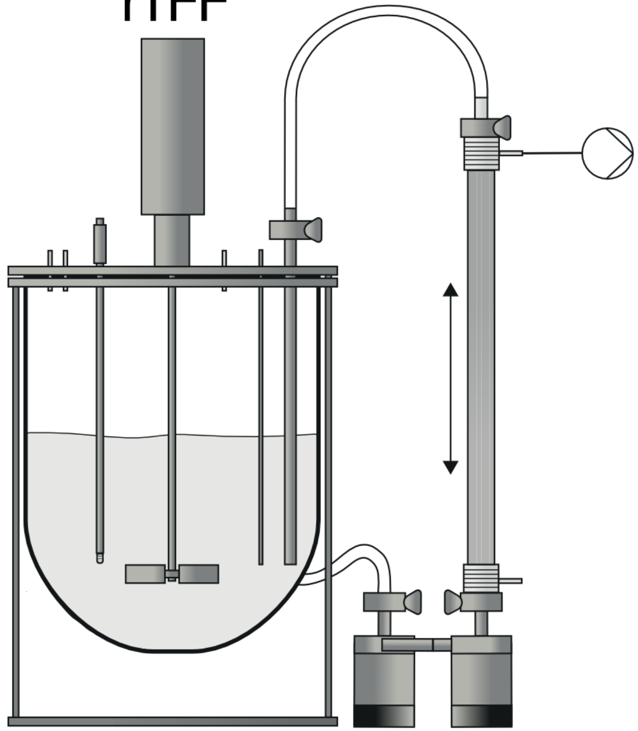
Push - Pull

rTFF: Bubble removal (Option 1)

Better Pumps for Better Yield!

Considerations:

- Ideal positioning of bubble removal (especially at smaller scales) consists in setups where pump outlets face to each other. Such, bubbles that are trapped in the running pumphead will be removed upon switching to the other pump.
- Ideally, the pump inlets are positioned vertically such that air bubbles can easily escape the pump head once the other pump is active
- At larger scale, the positioning is less critical, depending on the customer setup

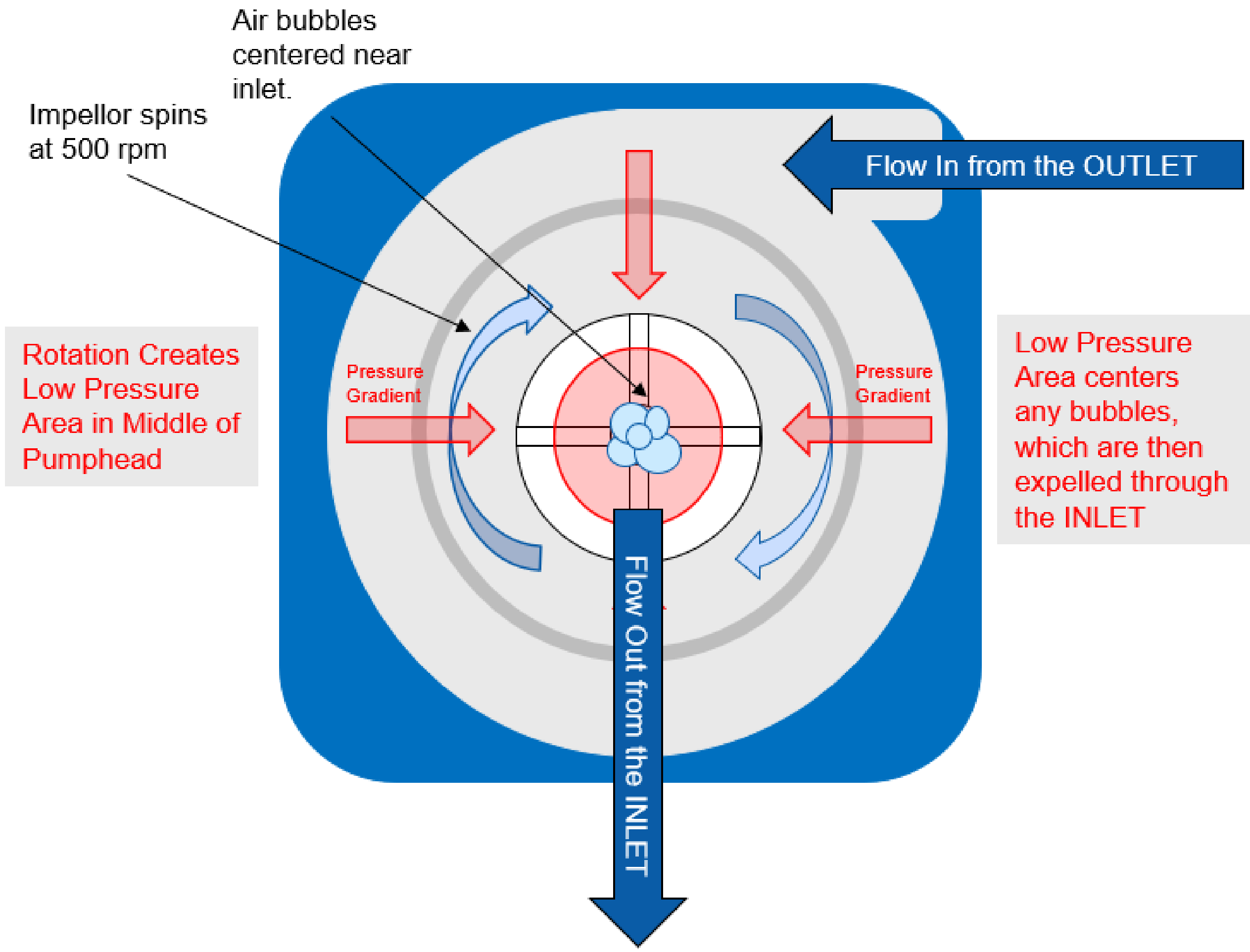


Pumps with outlets facing to each other and pump inlets positioned vertically for optimal bubble removal

rTFF: Bubble removal (Option 2)

Low-RPM Bubble Centering

- By operating the pump inversely integrated into the current flow direction at a low rpm, bubbles are centered and can easily be removed.
- Phase time can be modified, below times serve just as example

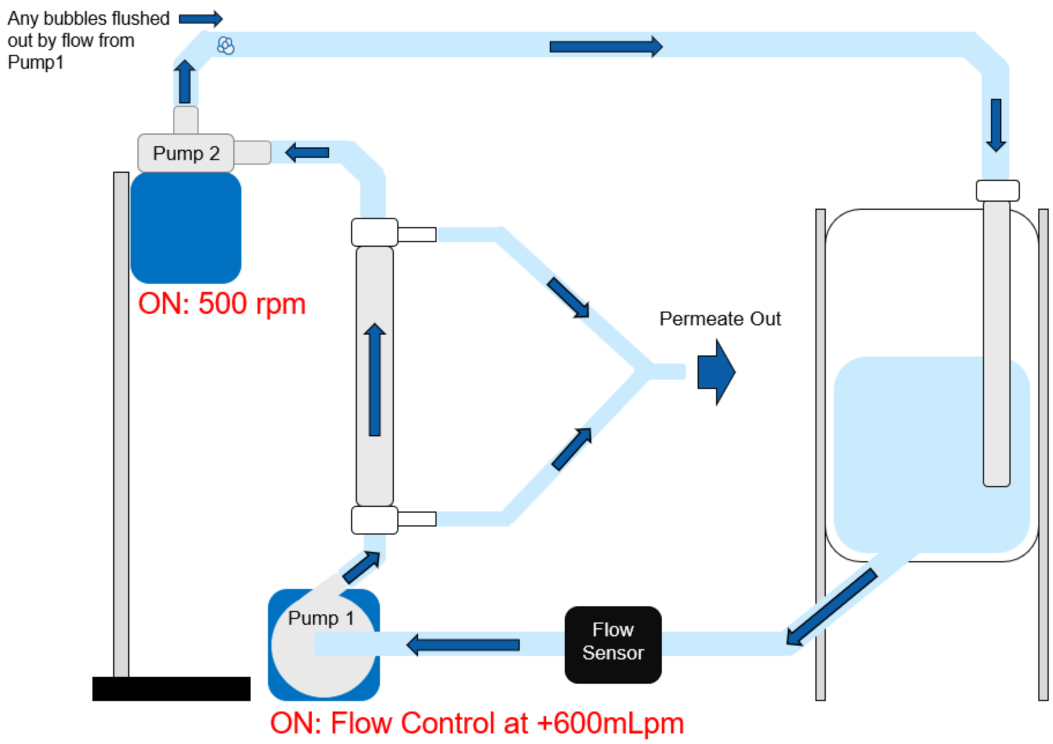


Low-RPM Bubble Centering (Phase A)

Better Pumps for Better Yield!

Phase A: “Forward” Flow control – Total Duration of 20s

- Pump 1 runs in flow control at 600 mlpm
- Pump 2 runs in speed mode at 500 rpm

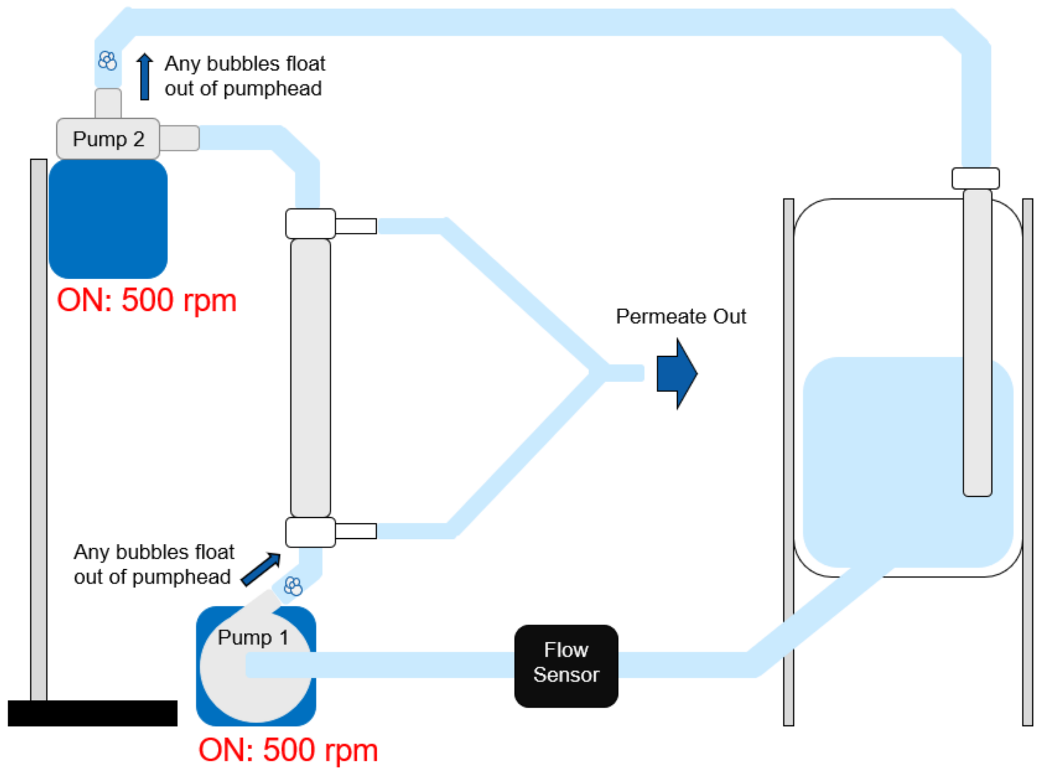


Low-RPM Bubble Centering (Phase B)

Better Pumps for Better Yield!

Phase B: Pause 1 – Total Duration of 1s

- Pump 1 runs in speed mode at 500 rpm
- Pump 2 runs in speed mode at 500 rpm

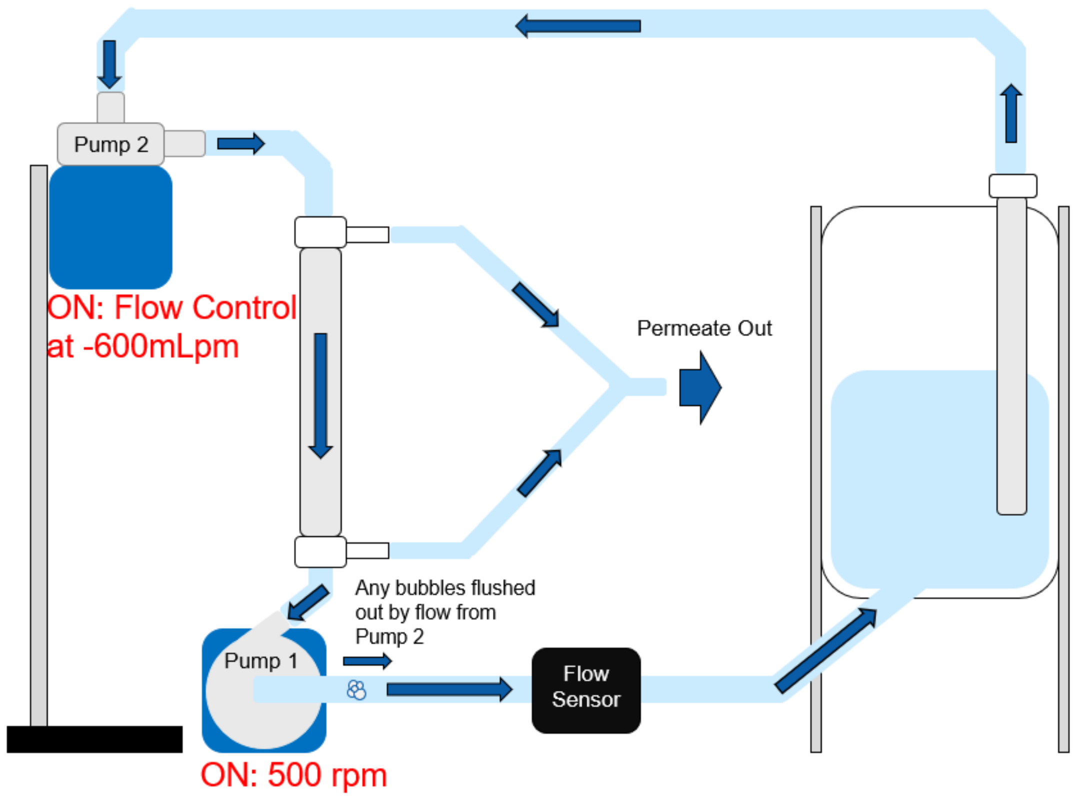


Low-RPM Bubble Centering (Phase C)

Better Pumps for Better Yield!

Phase C: “Reverse” Flow control – Total Duration of 20s

- Pump 1 runs in speed mode at 0 rpm
- Pump 2 runs in flow control at 600 mlpm

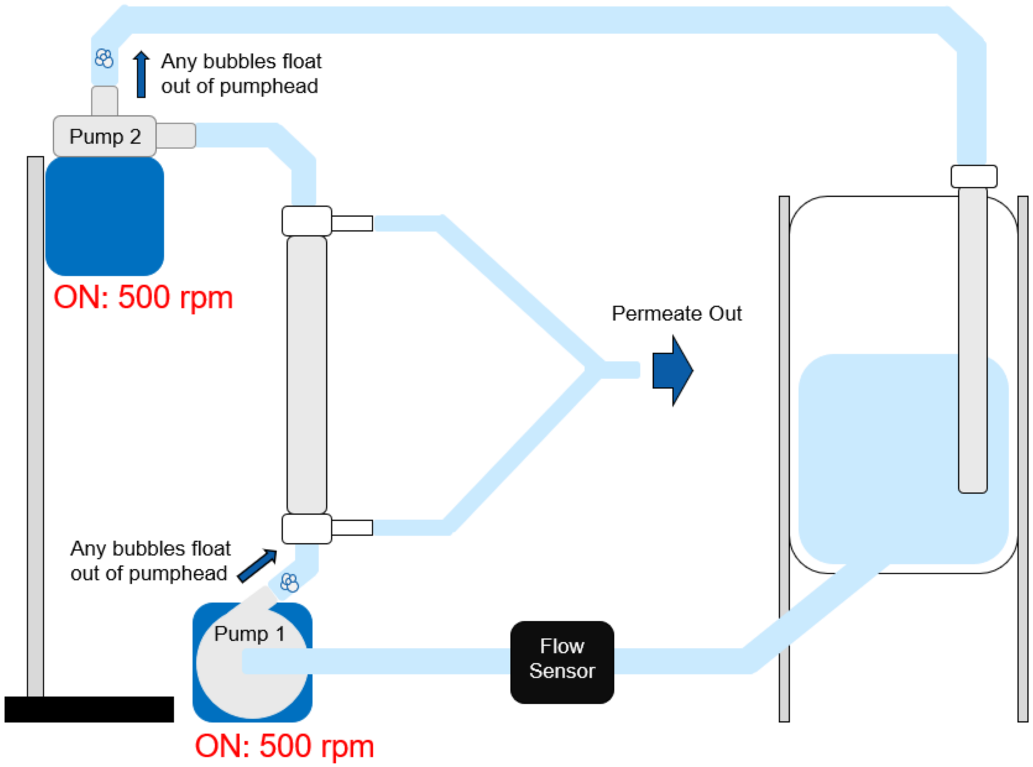


Low-RPM Bubble Centering (Phase D)

Better Pumps for Better Yield!

Phase D: Pause 2 – Total Duration of 1s

- Pump 1 runs in speed mode at 500 rpm
- Pump 2 runs in speed mode at 500 rpm

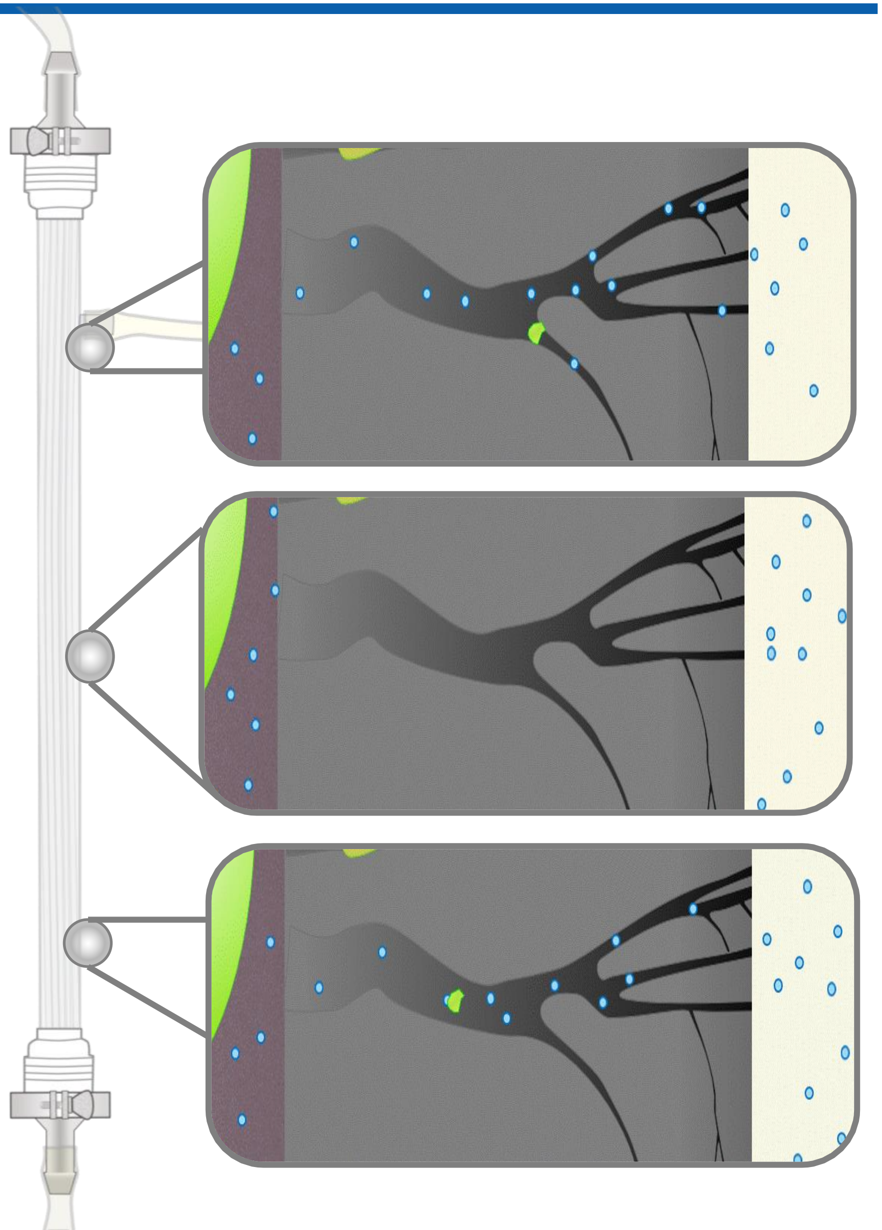


Backflushing is not for free!

Better Pumps for Better Yield!

The price for backflushing:

- Everything that flows back must be filtered at the other filter side (Starling Recirculation)
- Despite gel layer removal, high filtration flux might cause pore blocking over time
- Blocked pores might stay blocked
- Controlling Starling Recirculation can be beneficial also in rTFF (reduced crossflow (shear), larger lumen ID, shorter filter modules, etc.)

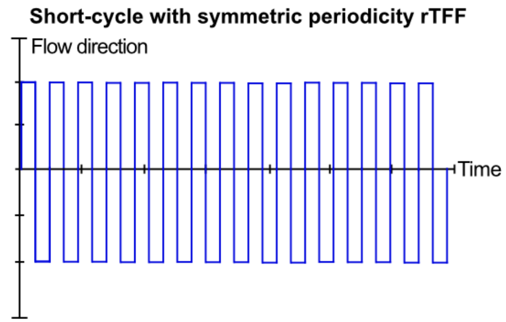


Various rTFF Cycle Time Strategies

Better Pumps for Better Yield!

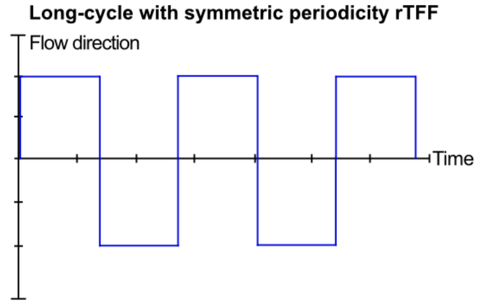
Standard rTFF: Short and equal cycle time (similar to ATF)

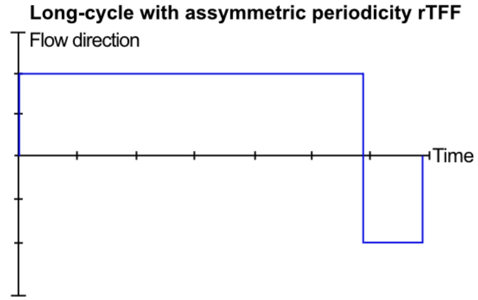
- Short cycle times with a cycle time of seconds to minutes. Cycle times can be of similar length, or different length. The crossflow might be similar for both phases, or different. It is possible to run at a certain crossflow for a certain time and integrate flushing at higher (or lower) crossflow from time to time.



Long-cycle with symmetric/asymmmetric periodicity rTFF: Very long and equal/unequal cycle times (hours to days)

- Long cycle times with a duration of minutes to hours, or even days. Cycle times can be of similar length, or different length. The crossflow might be similar for both phases, or different. It is possible to run at a certain crossflow for a certain time and imtegrate flushing at higher (or lower) crossflow from time to time.



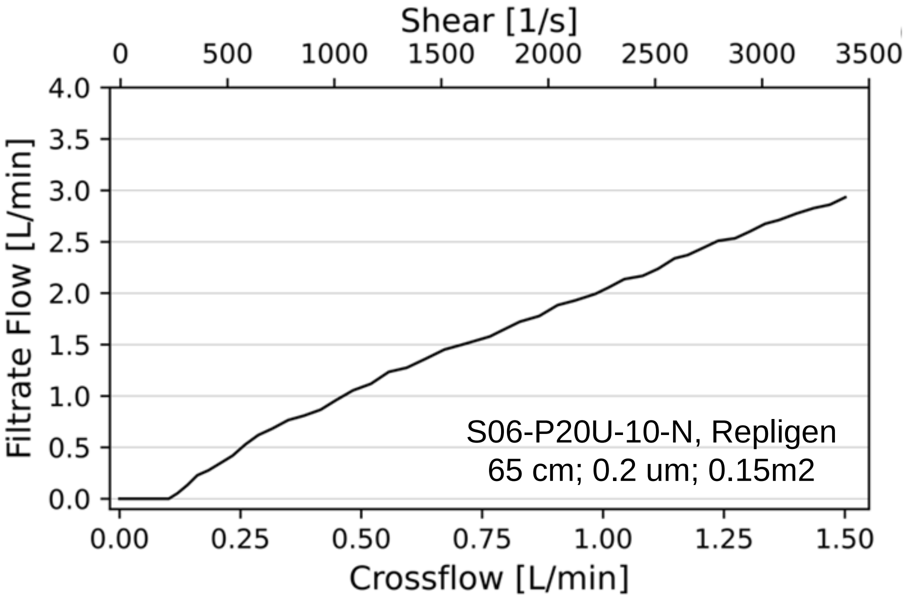


→ No limitation in cycle time in contrast to diaphragm pumps (which are limited by their hold volume)

Backup Slides

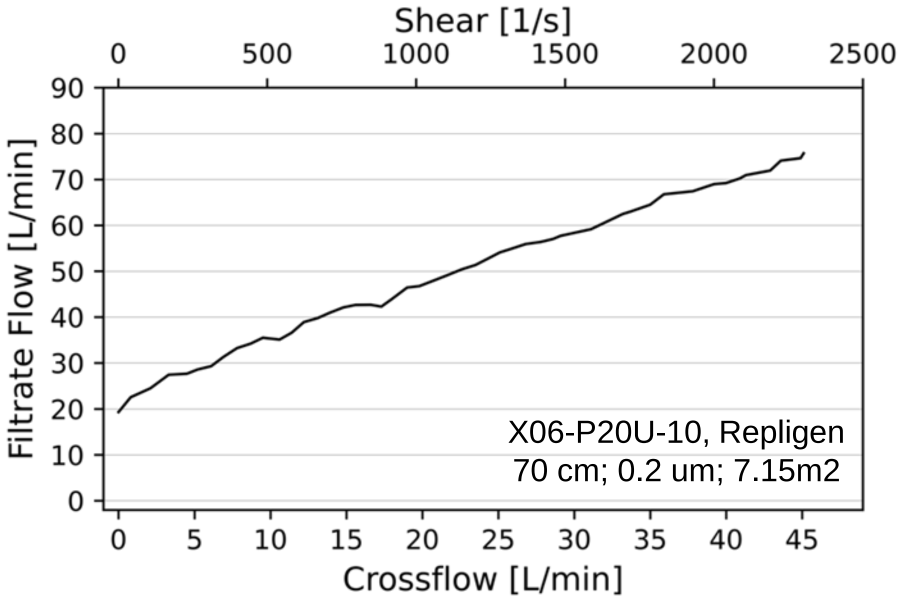
Crossflow vs. Co-current Filtrate Flow

Lab-scale



- Filtrate flow ≈ 2x Crossflow

Large-scale



- Filtrate flow ≈ 2x Crossflow

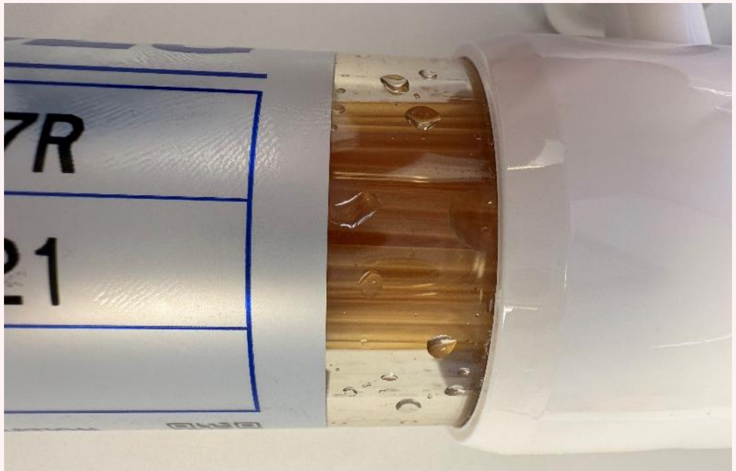
Crossflow vs. Co-current Filtrate Flow

Better Pumps for Better Yield!

→ Hollow Fibers were not designed for HPTFF, still most work very well!

Good Filter:

- High filtrate resistance
- Densly packed fibers
- Optimization in the coflow inlet and an optimal liquid distribution shield could be beneficial and might protect fibers, especially at larger scale



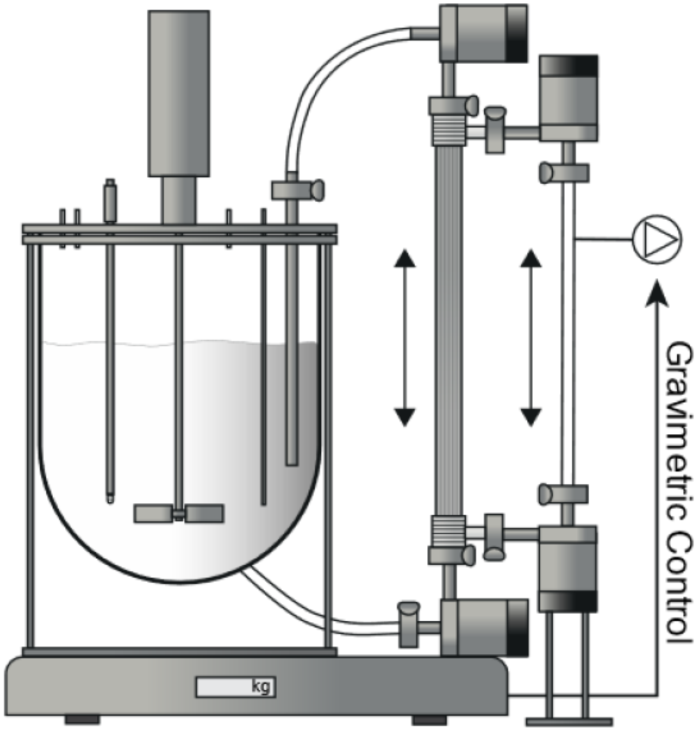
Not Ideal Filter:

- Low filtrate resistance
- Loose fibers or large gaps betwen fibers and housing

The ultimate TFF System (rscTFF)

Better Pumps for Better Yield!

Imagine: Alternating crossflow with alternating co-current filtrate flow …



rscTFF:

- No risk for inlet blocking
- Best possible Sieving performance
- Highest operational flexibility

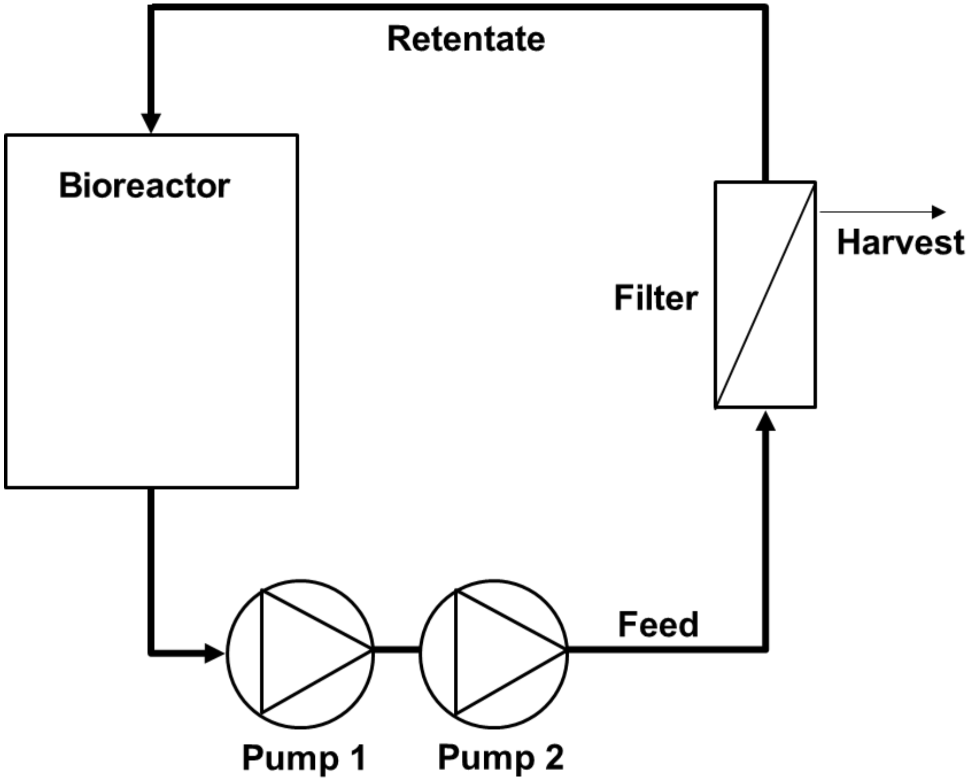
→ 4 pump system for now (high complexity)

→ 2 pumps if pumps could pump both directions

Low rpm TFF System

Better Pumps for Better Yield!

Reduction or rpm (potentially shear stress) by putting at least two pumps in series (this applies to all the before mentioned systems (TFF, HPTFF, rTFF, scTFF and rscTFF variants))



Centrifugal pumps can be put in series. By doing so:

- Achieving redundancy in case one system fails
- Reduction of rpm per pump to reach a setpoint pressure

Option 1: Pumps running at the same time at same speed

Option 2: 1 pump running on flow control other pumps acting as booster

Low rpm TFF System

Better Pumps for Better Yield!

Reduction or rpm (potentially shear stress) by putting at least two pumps in series (this applies to all the before mentioned systems (TFF, HPTFF, rTFF, scTFF and rscTFF variants)) Pumps can also be all in front of the filter (feed side), after the filter (retentate side) or before and after (feed and retentate side). More than one pump can also be used in the coflow loop.